MAJOR ARTICLE

Combination Polyene-Caspofungin Treatment of Rhino-Orbital-Cerebral Mucormycosis

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(See the editorial commentary by Walsh and Kontoyiannis on pages 372–4)

Background. It has been axiomatic that echinocandins (e.g., caspofungin) are ineffective against mucormycosis. However, on the basis of preclinical data, we recently began treating rhino-orbital-cerebral mucormycosis (ROCM) with combination polyene-caspofungin therapy.

Methods. To determine the impact of polyene-caspofungin therapy, ROCM cases identified by an *International Classification of Diseases, Ninth Revision* search were retrospectively reviewed to gather data on demographic characteristics, clinical history, and outcomes. The predefined primary end point was success (i.e., the patients was alive and not in hospice care) at 30 days after hospital discharge.

Results. Forty-one patients with biopsy-proven ROCM were identified over 12 years; 23 (56%) of these patients were Hispanic, and 34 (83%) were diabetic. Patients treated with polyene-caspofungin therapy (6 evaluable patients) had superior success (100% vs. 45%; $P = .02$) and Kaplan-Meier survival time ($P = .02$), compared with patients treated with polyene monotherapy. Patients treated with amphotericin B lipid complex had inferior success (37% vs. 72%; $P = .03$) and a higher clinical failure rate (45% vs. 21%; $P = .04$), compared with patients who received other polyenes. However, patients treated with amphotericin B lipid complex plus caspofungin had superior success (100% vs. 20%; $P = .009$) and survival time ($P = .01$), compared with patients who received amphotericin B lipid complex alone. The benefit of combination therapy, compared with monotherapy, was most pronounced in patients with cerebral involvement (success rate, 100% vs. 25%; $P = .01$). In multivariate analysis, only receipt of combination therapy was significantly associated with improved outcomes (odds ratio, 10.9; 95% confidence interval, 1.3–∞; $P = .02$).

Conclusions. Combination polyene-caspofungin therapy represents a promising potential alternative to polyene monotherapy for patients with ROCM. Randomized, prospective investigation of these findings is warranted.

Rhino-orbital-cerebral mucormycosis (ROCM) is a life-threatening infection that occurs most frequently in patients with diabetic ketoacidosis or in patients who are immunocompromised as a result of neutropenia or immunosuppressive drugs [1, 2]. Unfortunately, despite disfiguring surgical debridement and polyene antifungal therapy, the overall mortality of ROCM remains $\geqslant$50%, particularly in the presence of CNS extension. Because of the increasing incidence of mucormycosis [3–5] and the unacceptably high mortality rate associated with it, novel antifungal therapies are urgently needed.

Amphotericin B deoxycholate (AmB) and its lipid formulations remain the only antifungal agents approved for the treatment of invasive mucormycosis. Echinocandins have had no activity in in vitro susceptibility assays against the Mucorales [6–8]. Therefore, it has been axiomatic that echinocandins are ineffective in treating mucormycosis. However, traditional susceptibility testing may not reflect the true activity of echinocandins against molds in general and against the agents of mucormycosis in particular [9–11]. We recently reported that *Rhizopus oryzae,* the most common pathogen causing mucormycosis, expressed the target enzyme for echinocandins (1,3-β-glucan synthase, encoded by the *FKS* gene); that caspofungin inhibited the

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enzyme's activity in vitro; and that caspofungin had activity in the diabetic mouse model of disseminated mucormycosis [12]. Furthermore, combination therapy with caspofungin and amphotericin B lipid complex (ABLC) was synergistic in the same model [13].

On the basis of these data, we recently began treating ROCM with combination polyene-caspofungin therapy. We retrospectively reviewed cases of ROCM to compare outcomes of patients treated with combination therapy with those of patients not treated with combination therapy. In addition, we sought to determine whether outcomes differed by the initial polyene used for treatment.

METHODS

Chart abstraction. Cases of ROCM in patients hospitalized at Harbor–University of California at Los Angeles Medical Center (a tertiary care, public teaching hospital) and the University of California at Los Angeles Center for the Health Sciences (a tertiary care, private teaching hospital) were identified by searching hospital databases for *International Classification of Diseases, Ninth Revision* code 117.7 (zygomycosis and mucormycosis) from 1994 through 2006. All cases involving disease of the sinuses, orbit, and/or CNS (i.e., ROCM) were included in the study. Charts were abstracted with a standard form to gather data on demographic characteristics, clinical history, medications, and outcomes. The study was approved by institutional review boards at both medical centers.

Definitions and analyses. The predefined primary end point was success at 30 days after hospital discharge in patients treated with polyene monotherapy versus up-front (i.e., before clinical progression while receiving a previous regimen) polyene-caspofungin combination therapy. Success was defined as the patient being alive and not receiving hospice care. For the primary end point, patients without follow-up data available were considered to be nonevaluable; in secondary analyses, these patients were considered to have experienced clinical failure and were evaluated. As secondary end points, success and Kaplan-Meier time-to-death analyses were compared among patients treated with different antifungal regimens. The effect of a variety of demographic characteristics and clinical factors on survival was defined. Finally, radiographic findings and surgical treatment results were evaluated.

Statistics. Fisher's exact test, the χ^2 test, the Mann-Whitney *U* test, or the Wilcoxon signed rank test was used, as appropriate, to compare demographic characteristics, clinical factors, and outcomes. The log-rank test was used to compare time to death. Logistic regression bivariate (MedCalc) and multivariate analyses (SPSS) were used to define the effect of demographic characteristics and clinical factors on survival. For all analyses, 2-tailed *P* values $\leq .05$ were considered to be statistically significant.

RESULTS

Cases of mucormycosis. A total of 41 cases of rhino-orbital mucormycosis ($n = 21$) or ROCM ($n = 20$) were identified (table 1). One patient with ROCM also had pulmonary mucormycosis, and 1 patient each with rhino-orbital mucormycosis had coexisting cutaneous and pulmonary disease. All patients had mucormycosis proven by histopathologic examination of a biopsy specimen, in accordance with Mycosis Study Group-European Organization for the Research and Treatment of Cancer criteria [14].

The patients were predominantly male and Hispanic (table 1), and all had risk factors for ROCM, including diabetes mellitus (83% of patients), cancer (34%), active corticosteroid therapy (46%), neutropenia (12%), and transplantation (10%; 2 kidney transplantations and 2 hematopoietic stem cell transplantations) (table 1). Overall, 59% of patients had positive culture results; 19 cultures yielded *Rhizopus* species, and 1 culture yielded *Rhizomucor* species (for 4 cultures, the organisms were not identified).

Seventy-five percent of patients survived through hospital discharge, and 54% were alive and not receiving hospice care 30 days after hospital discharge. More patients were treated initially with ABLC ($n = 22$) than with AmB ($n = 15$) or with liposomal AmB (LAmB; $n = 4$). Seven patients (17%) were treated with up-front combination therapy with caspofungin plus a polyene (5 patients were treated with ABLC, and 2 were treated with LAmB).

The median daily doses of initial treatment with AmB, ABLC, and LAmB were 1 mg/kg (range, 0.3–1.5 mg/kg), 5 mg/kg (range, 5–10 mg/kg), and 5 mg/kg (range, 5–10 mg/kg/d), respectively. The median total doses of initial treatment with AmB, ABLC, and LAmB were 0.7 g (range, 0.05–1.75 g), 7.4 g (range, 0.3–28 g), and 34 g (range, 0.25–90 g), respectively ($P < .05$, for LAmB vs. AmB, LAmB vs. ABLC, and ABLC vs. AmB). Eight patients stopped initial AmB treatment because of nephrotoxicity, 4 patients stopped because of clinical failure (i.e., death or progression of infection), 2 patients stopped because of change of venue (i.e., transfer of care from an outside facility or to a new clinical service), and 1 patient was lost to follow-up. Two patients initially treated with LAmB stopped therapy because they were cured, and 2 patients stopped therapy because of change of venue. In contrast, 10 patients stopped initial ABLC treatment because of clinical failure, 5 stopped because of change of venue, 4 were cured, and 3 were lost to follow-up.

Diabetes mellitus and mucormycosis. Twenty (59%) of the 34 patients with diabetes mellitus had a known history of the disease at their presentation with mucormycosis. In particular, 14 (41%) of the diabetic patients were receiving corticosteroid therapy, 4 (29%) of whom had a known history of diabetes. Sixteen patients (47%) were receiving no medication for their

Table 1. Summary of 41 cases of rhino-orbital-cerebral mucormycosis (ROCM).

Variable	Patients (n = 41)
CNS involvement	20 (49)
Age, median years (range)	51 (4–83)
Male sex	24 (59)
Hispanic ethnicity	23 (56)
Duration of hospitalization, median days (range)	34 (4–120)
Transferred from outside the hospital	24 (59)
Risk factor	
Diabetes mellitus	34 (83)
Cancer	14 (34)
Corticosteroid therapy	19 (46)
Transplantation	4 (10)
Neutropenia	5 (12)
Proven disease[a]	41 (100)
Positive culture result	24 (59)[b]
Absolute neutrophil count, median ×1000 cells/μL (range)	11 (0.01–26.5)
Baseline creatinine level, median mg/dL (range)	1 (0.4–6.8)
Baseline BUN level, median mg/dL (range)	20 (8–128)
Up-front combination caspofungin therapy	7 (17)
Salvage combination caspofungin therapy	2 (5)
First polyene received	
Amphotericin B deoxycholate	15 (37)
Amphotericin B lipid complex	22 (54)
Liposomal amphotericin B	4 (10)
Duration, median days (range)	
From symptoms to presentation	5 (0–150)
From symptoms to diagnosis	9 (0–151)
From symptoms to antifungal treatment	9 (0–151)
From symptoms to first surgical procedure	9 (0–154)
From presentation to antifungal treatment	3 (0–44)
From presentation to first surgical procedure	4 (0–47)
Follow-up	61 (6–3613)
Success at	
Discharge from the hospital	31 (76)
30 days after discharge from the hospital[c]	20 (54)
1 year after discharge from the hospital[d]	15 (44)

NOTE. Data are no. (%) of patients, unless otherwise indicated. BUN, blood urea nitrogen.

[a] By Mycosis Study Group-European Organization for the Research and Treatment of Cancer criteria [14].

[b] Nineteen cultures yielded *Rhizomucor oryzae,* 1 culture yielded *Rhizomucor* species, and species were not identified for 4 cultures.

[c] Data are for 37 patients, because 4 patients were lost to follow-up before 30 days after hospital discharge.

[d] Data are for 34 patients, because 3 patients were lost to follow-up between 30 days and 1 year after hospital discharge.

diabetes at the time of presentation. Only 3 (21%) of the 14 patients with corticosteroid-induced diabetes were receiving medication for diabetes. Overall, 13 (42%) of 31 diabetic patients were acidotic at presentation (defined as bicarbonate level <20 mg/dL; bicarbonate levels at presentation were not available for 3 patients), and 12 (39%) of 31 patients had anion gaps >12 mEq/L at presentation.

Treatment-related outcomes. Four patients (1 who received combination therapy and 3 who received monotherapy) were lost to follow-up before 30 days after hospital discharge and were considered to be nonevaluable for the primary end point. None of those 4 patients had CNS disease, and all were lost to follow-up, because they were transferred back to their primary physicians at outside hospitals, from which records

Table 2. Success at 30 days after hospital discharge, by initial treatment.

	Proportion of patients (%)			Proportion of patients (%)			Proportion of patients (%)		
Patients	Monotherapy	Combination therapy	*P*	ABLC	AmB or LAmB	*P*	ABLC	ABLC plus caspofungin	*P*
Evaluable	14/31 (45)	6/6 (100)	.019	7/19 (37)	13/18 (72)	.029	3/15 (20)	4/4 (100)	.009
All	14/34 (41)	6/7 (86)	.040	7/22 (32)	13/19 (68)	.018	3/17 (18)	4/5 (80)	.021
With CNS disease	4/16 (25)	4/4 (100)	.015	3/12 (25)	5/8 (63)	.113	1/10 (10)	2/2 (100)	.047

NOTE. "Evaluable" includes 37 patients who had follow-up data available at 30 days after hospital discharge. "All" includes 4 additional patients who were lost to follow-up before 30 days after hospital discharge who were considered to have experienced clinical failure. No patients with CNS disease were lost to follow-up. ABLC, amphotericin B lipid complex; AmB, amphotericin B deoxycholate; LAmB, liposomal AmB.

were not available. Treatment with combination therapy was successful for all evaluable patients at 30 days after hospital discharge, compared with a success rate of 45% among patients treated with polyene monotherapy ($P = .02$, by Fisher's exact test) (table 2). Inclusion (as having experienced clinical failure) of the 4 patients who were lost to follow-up before 30 days after hospital discharge did not significantly alter the results (tables 2). The success rate among patients with CNS disease who were treated with combination therapy was 100%, compared with 25% among those treated with monotherapy ($P = .01$). There was no statistically significant difference in any demographic factor or measure of disease severity between patients treated with combination therapy and those treated with polyene monotherapy (table 3).

Patients treated initially with ABLC had a significantly lower success rate at 30 days after hospital discharge than did those treated initially with AmB or LAmB (table 2). The difference in success rates was driven by patients with CNS infection (table 2). However, the success rate of initial treatment with ABLC plus caspofungin was not significantly different from that of treatment with AmB or LAmB (100% [4 of 4 patients] vs. 72% [13 of 18 patients]; $P = .5$) and was superior to that of treatment with ABLC alone (table 2).

Different antifungal strategies were used during the 3 following periods of the study: 1992–1997 (before lipid amphotericin use), 1998–2003 (lipid amphotericin use but no combination therapy use), and 2004–2006 (combination therapy use) (table 4). However, overall outcomes did not significantly differ by study period.

In bivariate analyses of demographic characteristics and clinical factors, 4 variables were found to be associated with success at 30 days after hospital discharge; use of up-front combination therapy was directly associated with success, and the maximum creatinine level, the use of ABLC as initial polyene therapy, and CNS disease were inversely associated with success (table 5). In multivariate analysis, only combination therapy remained associated with success (table 5).

Finally, patients treated with combination therapy had superior Kaplan-Meier survival times, compared with patients treated with monotherapy (figure 1). In contrast, patients treated with ABLC had inferior Kaplan-Meier survival times, compared with patients treated with AmB, LAmB, or combination ABLC plus caspofungin therapy (figure 1).

Effect of antifungal therapy on creatinine level. During antifungal therapy, maximum and final creatinine levels increased (median increase, 1.6 and 0.5 mg/dL, respectively), compared with paired baseline creatinine levels ($P < .001$, for both comparisons by Wilcoxon signed rank test). Twenty-three (56%) of 41 patients experienced a doubling of their serum creatinine level during therapy. There was no statistically significant difference among patients treated initially with AmB, ABLC, or LAmB in baseline creatinine level, maximum creatinine level, last creatinine level, change in creatinine level from baseline to maximum or from baseline to last creatinine level, or frequency of doubling of creatinine level (data not shown).

Radiology and surgery. The sensitivities of initial CT (36 patients) and MRI (15 patients; 10 patients received both) for detecting sinusitis were 97% and 100%, respectively. However, initial MRIs were significantly more sensitive than CTs for detecting disease beyond the sinuses (86% vs. 33%; $P < .001$), in the orbit (47% vs. 19%; $P = .05$), and in the CNS (80% vs. 13%; $P = .001$).

All patients underwent surgical debridement. Ten (25%) of the 40 initial surgical procedures revealed no necrosis or eschar. Patients underwent a median of 2 surgical procedures (range, 1–6 surgical procedures). Complete orbital exenteration was performed for 24 (59%) of the 41 patients but was not associated with improved survival ($P = .2$). Survival was not altered on the basis of whether exenteration was performed during the first, second, or third surgical procedure (data not shown).

DISCUSSION

Echinocandins have no activity against the fungi that cause mucormycosis in standard in vitro susceptibility tests. However, molecular and laboratory animal studies revealed that *R. oryzae* expressed the target enzyme for echinocandins and that caspofungin was synergistic with ABLC for the treatment of mice with mucormycosis including extensive brain involvement [12, 13]. We now report that patients with ROCM who are treated

Table 3. Comparison of patients who received combination therapy with patients who received monotherapy.

Characteristic	Patients		P
	Received combination therapy (n = 7)	Received monotherapy (n = 34)	
Age, median years (range)	42 (27–69)	55 (4–83)	.3
Male sex	5 (71)	19 (56)	.4
Hispanic ethnicity	4 (57)	19 (56)	.6
Risk factor			
Diabetes	6 (86)	28 (82)	.7
Cancer	1 (14)	13 (38)	.2
Corticosteroid therapy	2 (28)	17 (50)	.3
Transplantation	0 (0)	4 (12)	.5
Glucose level, median mg/dL (range)	330 (154–449)	310 (80–1442)	.9
Bicarbonate level, median mg/dL (range)	14 (7–30)	24 (5–31)	.2
Acidotic (bicarbonate level < 20 mg/dL)[a]	4 (66)	9 (28)	.1
Anion gap, median mEq/L (range)	17 (7–27)	12 (5–24)	.2
Absolute neutrophil count, median ×1000 cells/μL (range)	9.4 (3.3–16.2)	11.4 (0.01–24.9)	.9
Neutropenia (ANC, ⩽500 cells/μL)	0 (0)	4 (12)	.5
BUN level, median mg/dL (range)	14 (8–20)	23 (7–128)	.1
Baseline creatinine level, median mg/dL (range)	0.8 (0.5–1.1)	1.1 (0.4–6.8)	.1
Maximum creatinine level, mg/dL (range)	1.9 (0.7–5.6)	2.4 (0.7–9.8)	.1
Creatinine level doubled	4 (57)	19 (56)	.9
Time to presentation, median days (range)	5 (0–45)	6 (0–150)	.9
Time to diagnosis, median days (range)	7 (1–54)	9 (0–151)	.7
Time to treatment, median days (range)	7 (2–54)	10 (0–151)	.7
Time to surgery, median days (range)	10 (6–58)	9 (0–154)	.6
CNS disease	4 (57)	16 (47)	.5
ABLC initial therapy	5 (71)	17 (50)	.1

NOTE. Data are no. (%) of patients, unless otherwise indicated. ABLC, amphotericin B lipid complex; ANC, absolute neutrophil count; BUN, blood urea nitrogen.

[a] Data are for 6 patients who received combination therapy and 32 patients who received monotherapy, because 1 patient who received combination therapy and 2 patients who received monotherapy did not have bicarbonate levels available.

with combination polyene-caspofungin had significantly improved outcomes 30 days after hospital discharge and improved long-term survival, compared with patients treated with polyene monotherapy. Whether this benefit of combination therapy is specific to caspofungin or reflects a class effect of echinocandins is unclear, although data from the mouse model suggest that other echinocandins might also be synergistic with lipid polyenes for the treatment of mucormycosis [15]. Although patients treated with combination ABLC-caspofungin therapy had superior outcomes, compared with patients treated with ABLC alone, an insufficient number of patients was treated with LAmB to make conclusions about combination therapy with the latter polyene.

There are 3 possible mechanisms by which addition of an echinocandin may improve the efficacy of polyene therapy for mucormycosis: (1) disruption of β glucan cross-linking of the cell wall [16, 17], leading to enhanced polyene delivery to the cell membrane; (2) altered virulence of the fungus, either by stunting filamentation [11] or altering cell wall content [18]; and (3) enhanced host response to the fungus [19–21]. Investigation into the mechanism of action of echinocandin combination therapy is ongoing.

ABLC had inferior CNS penetration, compared with LAmB or AmB, in a rabbit model [22], suggesting that it may be a less desirable option for the treatment of mucormycosis with CNS extension [1]. Our data reveal that patients with ROCM who were treated with ABLC had lower success rates than those treated with either AmB or LAmB and that the effect was driven by clinical failure experienced by patients with CNS involvement. However, in multivariate modeling, only combination therapy was significantly associated with improved survival.

To our knowledge, the strong link that we found between ROCM and Hispanic ethnicity has not been previously reported. The predominance of Hispanic patients was dispro-

Table 4. Success at 30 days after hospital discharge among evaluable patients, by antifungal therapy and study period.

	Proportion of patients with success (%), by study period			
Antifungal therapy	1992–1997	1998–2003	2004–2006	*P*
AmB	3/5 (60)	5/8 (63)	1/1 (100)	
ABLC	…	2/9 (22)	1/6 (17)	
ABLC plus caspofungin	…	…	4/4 (100)	
LAmB	…	1/1 (100)	1/1 (100)	
LAmB plus caspofungin	…	…	2/2 (100)	
Total	3/5 (60)	8/18 (44)	8/14 (57)	.7

NOTE. The period 1992–1997 was before lipid amphotericin (AmB) was used. During the period 1998–2003, lipid AmB was used, but combination therapy was not used. During the period 2004–2006, combination therapy was used. ABLC, AmB lipid complex; LAmB, liposomal AmB.

portionate to the ~25% incidence of Hispanic ethnicity that we expected on the basis of demographic characteristics at the study hospitals. Whether this high frequency of Hispanic patients with ROCM reflects a higher incidence of diabetes mellitus in Hispanic persons relative to other ethnic groups or a unique host predisposition to ROCM aside from diabetes is not clear from our data and merits additional study.

In the largest case series of mucormycosis published to date, Roden et al. [2] noted that diabetes was the most common risk factor for mucormycosis (as in our study). However, a higher proportion of patients in the current series was diabetic, compared with in the former series (83% vs. 27%). The difference in background diabetes rates is likely because of our focus on patients with ROCM, which is strongly associated with diabetes [1]. In contrast, Roden et al. [2] reviewed mucormycosis of all sites. Furthermore, although mucormycosis was the diabetes-defining illness in 16% of patients in the previous series, 41% of diabetic patients in the current series had no known history of diabetes before their presentation with ROCM. In particular, patients in whom diabetes was associated with corticosteroid use had frequently not received diagnoses of diabetes and were almost always untreated for their diabetes before presentation. Thus, our data underscore the need for close monitoring of glucose levels in patients receiving corticosteroids, as well as the need to aggressively treat diabetes in such patients. In addition, less than one-half of diabetic patients were acidotic at presentation, and 25% of our patients had no evidence of necrosis or eschar during the initial surgical exploration. Thus, our data emphasize the need to maintain a high index of suspicion for mucormycosis in patients with the appropriate clinical syndrome, regardless of acid-base status or the initial appearance of tissue on gross inspection.

With respect to imaging studies, MRI was clearly more sensitive for detecting disease extension beyond the sinuses and for CNS disease in particular. Although CT was sensitive for revealing sinusitis, 1 patient with ROCM had normal initial CT findings, which again underscores the need to maintain a high index of suspicion in the right clinical context, regardless of the findings of initial imaging studies.

The need for complete orbital exenteration as a treatment of ROCM has never been adequately studied. Surgeons at our hospitals advocate a "conservative-aggressive" approach, in which all necrotic material is removed, but the limits of surgical debridement are defined by use of frozen sections intraoperatively, and when possible, uninvolved orbital structures are spared. Our data lend credence to the belief that total exenteration may not be necessary in every case and does not necessarily improve survival. Because of the retrospective nature of our study, we cannot exclude the possibility that extenteration was a marker for more-advanced disease, which could also explain why those who received exenteration did not have improved survival. Nevertheless, it is our recommendation that surgeons make real-time decisions regarding the extent of surgery required on the basis of intraoperative findings and frozen sections from debrided materials.

The major limitation of our study is its retrospective, observational nature. One source of potential bias in a retrospective study with historical controls is the changing management of the infection over the study period [23]. Indeed, most of the AmB use occurred during the period 1992–1997, lipid polyene monotherapy was predominantly used during the period 1998–2003, and all of the combination therapy occurred during the period 2004–2006. Partially mitigating the potential bias introduced by changes in antifungal therapy over time is the fact that outcomes did not improve over time (as revealed when comparing the 3 study periods). Furthermore, even during the period 2004–2006, combination therapy resulted in higher success rates than did monotherapy (100% vs. 25%). In addition, in contrast to antifungal therapy, surgical manage-

Table 5. Logistic regression analyses for success at 30 days after hospital discharge.

Analysis, variable	Survival OR (95% CI)	*P*
Bivariate		
Combination therapy	9.0 (1.1–∞)	.03
ABLC vs. AmB or LAmB initial treatment	0.2 (0.06–0.9)	.03
CNS disease	0.3 (0.07–1.1)	.07
Maximum creatinine level	0.7 (0.5–1.0)	.05
Multivariate		
Combination therapy	10.9 (1.3–∞)	.02
ABLC vs. AmB or LAmB initial treatment	0.2 (0.02–1.6)	.17
CNS disease	0.3 (0.04–2.2)	.33
Maximum creatinine level	0.9 (0.5–1.4)	.66

NOTE. ABLC, amphotericin B lipid complex;. AmB, amphotericin B; LAmB, liposomal AmB.

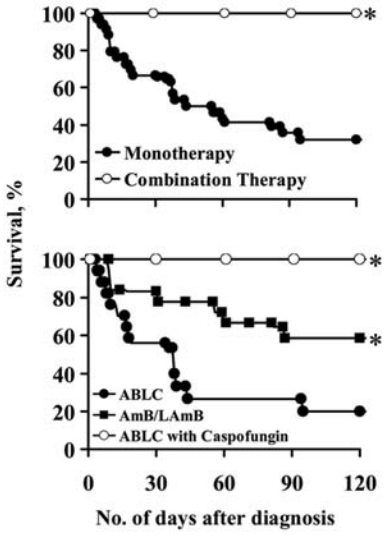

Figure 1. Kaplan-Meier survival curves for patients with rhino-orbital-cerebral mucormycosis treated with various antifungal agents. Asterisks (*) indicate $P < .05$, for comparison with monotherapy or amphotericin B lipid complex (ABLC). AmB, amphotericin B; LAmB, liposomal AmB.

ment did not significantly change over the study period, because the same group of attending surgeons performed all of the surgical procedures at both hospitals, with virtually no turnover. Finally, another limitation of the study was the limited number of neutropenic patients and transplant recipients, which made it difficult to evaluate the efficacy of combination therapy among those patients.

Nevertheless, our encouraging findings underscore the need for a prospective, randomized clinical trial to define the efficacy of combination echinocandin-polyene therapy for the treatment of ROCM. Until such data are available, it may be reasonable to consider combination echinocandin-polyene therapy for ROCM, given the unacceptably poor outcomes with polyene monotherapy, the lack of other agents licensed to treat the disease, and the well-established safety profile of the echinocandins.

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