Multicenter, Noncomparative Study of Caspofungin in Combination With Other Antifungals as Salvage Therapy in Adults With Invasive Aspergillosis

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BACKGROUND. Caspofungin inhibits synthesis of β-1,3-glucan, an essential component of the *Aspergillus* cell wall. This echinocandin has demonstrated efficacy (45% success) as salvage monotherapy of invasive aspergillosis (IA). Interest remains as to whether caspofungin, in combination with other antifungal classes, can improve the efficacy against IA.

METHODS. The study involved 53 adults with documented IA who were refractory to or intolerant of standard antifungal therapy and received caspofungin and 1 other mold-active antifungal agent (at the investigator's discretion). Efficacy was assessed by signs, symptoms, and radiographs at the end of combination therapy and Day 84 after combination therapy initiation. Favorable (complete or partial) responses required significant clinical and radiographic improvement. Diagnoses and outcomes were assessed by an independent expert.

RESULTS. Among the 53 patients enrolled the most common underlying diseases were acute leukemia (53%), lymphoma (11%), and chronic leukemia (6%). Pulmonary aspergillosis (81%) was the most common site, and most patients (87%) were refractory to prior therapy. Success at the end of combination therapy and Day 84 was 55% (29/53) and 49% (25/51), respectively. Fifty-seven percent of patients with neutropenia and 54% who received an allogeneic hematopoietic stem cell transplant responded favorably. Survival at Day 84 was 55%. Combination therapy, dosed on average for 31.3 days, was well tolerated. Two (4%) serious drug-related adverse events, both attributed to voriconazole, occurred. None of the patients discontinued caspofungin due to toxicity.

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CONCLUSION. Caspofungin in combination with a triazole or polyene was an effective alternative as salvage therapy for patients with recalcitrant *Aspergillus* infections. ***Cancer* 2006;107:2888–97.** © *2006 American Cancer Society.*

KEYWORDS: caspofungin, combination therapy, salvage therapy, aspergillosis.

The incidence of invasive fungal infections has risen dramatically over the last 3 decades.[1,2] *Aspergillus spp.* have become the second most common fungal pathogen encountered in the hospital setting, accounting for approximately 30% of the fungal infections in cancer patients. Certain prognostic factors associated with invasive aspergillosis (IA), including significant immunosuppression, disseminated infection, and failure of initial antifungal therapy, contribute to the poor outcome in these patients.[3–5]

Recently, several new antifungal agents have been licensed for the treatment of IA.[6] Lipid preparations of amphotericin B, voriconazole, and caspofungin have all demonstrated efficacy in animal models and patients with IA.[7–11] Nevertheless, IA is still associated with frequent failures and significant mortality. The prognosis is worse in patients receiving salvage therapy for refractory infections. Successful outcomes occur in less than half the patients receiving these newer agents as salvage monotherapy: amphotericin B lipid-complex 42%, voriconazole 39%, and caspofungin 45%.[7,9,11]

Hence, an interest in antifungal combinations, particularly with regimens targeting both the *Aspergillus* cell membrane (polyenes or triazoles) and cell wall (echinocandins), has emerged. Many in vitro and in vivo evaluations demonstrate an additive effect of such combination regimens.[12–14] Furthermore, the results of several retrospective studies in patients receiving caspofungin with either a polyene or triazole support further evaluation of combination therapy as salvage therapy of IA.[15,16] Currently, there are no published, prospective studies assessing the efficacy of an echinocandin with other antifungal agents for the treatment of IA. Herein we report data from a prospective study involving 53 patients receiving caspofungin in combination with either a triazole or a polyene as salvage therapy against documented cases of IA.

MATERIALS AND METHODS

Patient Population

This open-label, noncomparative, multicenter clinical trial was designed to assess the efficacy and safety of caspofungin in combination with triazoles or polyenes as salvage treatment for IA. The protocol was approved by the Institutional Review Boards of all participating centers. Written informed consent was obtained from all enrolled patients. The IA diagnosis, the effect of prior antifungal therapy, and the efficacy of combination therapy for all patients were reviewed and evaluated by an independent expert (T.F.P.), who did not participate as a study investigator.

Inclusion in this study required that adult patients, ≥16 years, have either definite or probable IA, per the criteria established by the European Organization for Research and Treatment of Cancer (EORTC) and the Bacterial and Mycosis Study Group BAMSG.[17] Consistent with those guidelines, a patient could also be diagnosed serologically by galactomannan sandwich enzyme-linked immunosorbent assay (ELISA) provided the patient had multiple (consecutive) blood samples for ELISA (titer cutoff >1.0) in association with the appropriate clinical, host, and radiographic findings. In addition, patients were required to demonstrate refractoriness or intolerance at therapeutic doses of standard antifungal therapy. Refractoriness was defined as progression of disease or failure to improve clinically and radiographically despite ≥7 days of standard therapy. Standard therapy included licensed, therapeutic doses of amphotericin B deoxycholate (≥0.75 mg/kg daily up to 1.5 mg/kg daily), lipid formulations of amphotericin B (≥3.0–5.0 mg/kg daily of liposomal amphotericin or ≥5.0 mg/kg daily of amphotericin B lipid complex), caspofungin (50 mg daily, after a 70-mg loading dose), itraconazole (intravenous [i.v.] ≥200 mg/day after 200 mg twice daily for 4 doses, or orally ≥400 mg/day), voriconazole (i.v. 8 mg/kg daily for voriconazole i.v. after having received 2 loading doses of 6 mg/kg, or orally ≥400 mg each day), or investigational triazoles (eg, posaconazole; at doses specified for the treatment of IA). Patients receiving caspofungin monotherapy during the prestudy period were only eligible if the maintenance dose was 50 mg daily. Prior combination therapy was permitted provided an echinocandin was not part of the initial regimen. Intolerance of standard therapy referred to the development of nephrotoxicity (defined as doubling of baseline serum creatinine or creatinine >2.5 mg/dL while receiving standard therapy), preexisting renal impairment (creatinine >2.5 mg/dL), or other

significant intolerance to prior therapy (eg, severe infusion-related reactions).

Exclusion criteria included a history of allergy or serious reaction to the agents used in the combination regimen or ongoing treatment with cyclosporin A. Abnormal laboratory values that disqualified patients from study participation were total serum bilirubin or serum transaminases (alanine transaminase [ALT] or aspartate aminotransferase [AST] of $\geq$5 times the upper limit of normal range [ULN], or International Normalization Ratio [INR] $>$ 2). Patients with noninvasive forms of aspergillosis were also ineligible.

Study Design

All patients received caspofungin together with $\geq$1 antifungal agent from either the triazole class (ie, itraconazole or voriconazole) or the polyene class (ie, amphotericin B deoxycholate or lipid amphotericin preparations). With the intent of maximizing the potential efficacy benefit against these recalcitrant cases of IA, a 70-mg daily dose of caspofungin was chosen; the decision was supported by the accumulating, encouraging safety experience at this higher dose. The choice and dose of the nonechinocandin agent was at the investigator's discretion. The study mandated that the nonechinocandin agent be licensed for use in IA and administered at least at the minimum approved dose for IA.

Duration of therapy was based on the severity of underlying disease, recovery from immunosuppression, and rapidity of clinical response. Generally, patients received combination therapy for a minimum of 28 days and at least 7 days after resolution of symptoms. Patients who achieved a favorable response (complete or partial response) after completion of combination therapy could either receive sequential therapy with caspofungin monotherapy or be placed on suppressive oral triazole therapy (with either itraconazole or voriconazole).

A detailed description of the infection was performed at baseline, twice weekly, and on the last day of combination therapy, and at Day 84 after combination therapy onset. Although it was anticipated that most of the patients would have completed combination therapy by Day 84, it was expected that some patients may have still been receiving combination therapy at the time of the Day 84 visit. All patients were evaluated 1 month after the completion of study therapy, and the subset of patients with a favorable response at each of the predetermined visits (including the 1-month posttherapy visit) were also seen at 3, 6, and 12 months after the completion of study therapy to assess for IA recurrence. Follow-up radiographs from relevant site(s) of infection were also collected periodically (at least monthly) to assess improvement or deterioration. Follow-up radiographic imaging was also obtained within a week before the end of combination therapy and at the Day 84 visit. Noninvasive samples, such as specimens for fungal culture or serum for galactomannan ELISA or polymerase chain reaction (PCR) were also collected at specified intervals during therapy.

Efficacy Assessment

The expert reviewer independently determined the diagnosis of IA, the reason for study entry (whether refractory or intolerant to prior therapy), and outcome at both the end of combination therapy (primary efficacy endpoint) and Day 84 after onset of combination therapy. The final expert assessments were used for all efficacy analyses in this report.

A 'favorable response' denoted either a complete or partial response. Complete response mandated resolution of all clinical signs and symptoms attributable to IA and complete resolution of radiographic or bronchoscopic abnormalities. 'Partial response' signified meaningful improvement of all clinical signs and symptoms attributable to IA and improvement ($\geq$50% reduction) of radiographic or bronchoscopic abnormalities. A partial response included cases wherein radiographic sequelae persisted (ie, persistent scar), regardless of the overall clinical or radiographic level of improvement. Patients were considered to have an 'unfavorable response' if they had either stable disease or failure. Irrespective of the response to subsequent therapy, patients who were counted as failures at the end of combination therapy were counted as failures at the Day-84 visit, provided the Day-84 visit occurred at that same or a later timepoint. Finally, recurrence indicated reemergence of IA after discontinuation of combination therapy.

Safety Assessment

Patients were monitored for clinical adverse events daily and for 14 days after the completion of caspofungin therapy (either as combination therapy or as sequential monotherapy). Laboratory tests were monitored twice weekly throughout the study therapy period and during the 14-day posttherapy follow-up. All adverse events were rated by the investigator as to their severity and the likelihood of their relation to study therapy. In addition, for each drug-related adverse event an effort was made to ascertain whether the investigator believed the event was related to caspofungin, the nonechinocandin component, or the combination.

TABLE 1
Baseline Patient Characteristics

	Caspofungin and amphotericin B formulation, N = 16	Caspofungin and Triazoles, N = 37	Overall, N = 53
	No. (%)	No. (%)	No. (%)
Sex			
Men	10 (63)	23 (62)	33 (62)
Women	6 (37)	14 (38)	20 (38)
Race			
Caucasian	15 (94)	35 (95)	50 (94)
Black	1 (6)	1 (3)	2 (4)
Asian	—	1 (3)	1 (2)
Age, y			
≤40	4 (25)	9 (24)	13 (25)
41 to 64	8 (50)	18 (49)	26 (49)
≥65	4 (25)	10 (27)	14 (26)
Median	53.5	55.0	54.0
Range	21–73	17–74	17–74
Site of *Aspergillus* infection (final diagnosis)			
Pulmonary	12 (75)	31 (84)	43 (81)*
Sinus	1 (6)	2 (5)	3 (6)†
Disseminated/multiple sites	3 (19)	4 (11)	7 (13)‡
Refractory or intolerant			
Refractory	12 (75)	34 (92)	46 (87)
Intolerant	4 (25)	3 (8)	7 (13)
Underlying disease			
Hematologic disorders	14 (88)	31 (84)	45§ (85)
Acute leukemias	6	21	27‖
Chronic leukemias	1	3	4¶
Lymphoma	4	2	6#
Other heme conditions	3	5	8**
Solid organ (lung) tranplant	—	1 (3)	1 (2)
Solid (lung) tumor	1 (6)	—	1 (2)
Corticosteroids	1 (6)	5 (14)	6 (11)
Neutropenic status (cells/mL) at study entry			
ANC <500	11 (69)	17 (46)	28 (53)
ANC ≥500	5 (31)	20 (54)	25 (47)

ANC indicates absolute neutrophil count.

* Includes 11 (21%) with definite pulmonary invasive aspergillosis (IA) and 32 (60%) with probable pulmonary IA. Among the 32 patients with probable infections, 14 were confirmed by sputum or broncheoalveolar lavage culture for *Aspergillus sp.* The remainder were confirmed serologically (via *Aspergillus* galactomannan ELISA [16] or PCR [2]).

† Includes 2 (4%) with definite sinus IA and 1 (2%) with probable sinus IA. The 2 cases of definite IA were confirmed histopathologically. The 1 patient with probable disease was confirmed serologically (via galactomannan ELISA).

‡ Includes 5 diagnosed by culture for *Aspergillus sp.* and 2 diagnosed by histopathologic means.

§ Seventeen (32%) patients were recipients of a hematopoietic stem cell transplantation (HSCT), including 13 (25%) patients who received an allogeneic HSCT.

‖ Includes 24 (45%) patients with AML and 3 (6%) patients with ALL.

¶ Includes 3 (6%) patients with CLL and 1 (2%) patient with hairy cell leukemia.

Includes 2 (4%) patients with Hodgkin's lymphoma, and 4 (8%) patients with NHL.

** Other hematological conditions included multiple myeloma (2 patients), myelodysplastic syndrome (2 patients), and aplastic anemia/medullary aplasia (4 patients).

Statistical Analysis

The design and sample size of this study were not intended to test specific hypotheses with regard to the efficacy. The primary evaluation for efficacy was the proportion of patients with a favorable response at the end of combination therapy. Efficacy was also assessed at Day 84 after combination therapy onset. For each proportion the 95% confidence interval (CI) was calculated as an exact CI based on the binomial distribution.

The primary efficacy population was prespecified as the adjudicated population, which was based on the independent expert's assessments. Inclusion in this population required that patients have a docu-

mented diagnosis of IA, receive ≥1 dose of combination therapy, and have an appropriate efficacy evaluation at the timepoint of interest. A secondary analysis focused on the subset of patients in the adjudicated population who received >7 days of combination therapy.

From a safety perspective, the study was designed to show that combination therapy would be well tolerated with respect to the development of serious, unanticipated, drug-related adverse events. For this study, an unanticipated adverse event was defined as an adverse event not expected to occur based on the clinical safety profile for each of the different antifungals included in the combination regimen, as described in the respective product circulars. With approximately 50 patients enrolled, the study could observe with ≥90% probability a serious unanticipated event with a true incidence of 5%. All patients who received ≥1 dose of combination therapy were included in safety analyses.

RESULTS

Enrollment Status

This trial was conducted in the US and Europe between February 2003 and July 2004. Eighteen investigators from 6 different countries enrolled a total of 53 patients. All 53 patients met the diagnostic criteria of IA and had data on which to base an outcome assessment.

Thirty-seven (70%) patients received caspofungin with a triazole, including 30 (57%) patients receiving caspofungin with voriconazole and 7 (13%) patients receiving caspofungin with itraconazole. Of the 16 patients receiving polyene therapy, 7 received amphotericin B lipid-complex, 5 received amphotericin B deoxycholate, and 4 received liposomal amphotericin.

Baseline Characteristics, Demographics, and Site of Infection

Most patients were male and of Caucasian origin (Table 1). The majority (85%) had hematologic disorders at study entry. Approximately one-third were recipients of either an autologous (4) or allogeneic (13) hematopoietic stem cell transplantation (HSCT). Neutropenia was present at the onset of combination therapy in 53% of patients.

The expert categorized all sites of infection according to the EORTC/BAMSG criteria (Table 1). Overall, 43 (81%) patients had pulmonary disease, including 11 definite and 32 probable cases. Of the remaining 10 patients, 3 had sinus aspergillosis and 7 had multiple (disseminated) sites of infection. Among the patients with disseminated infection were 2 patients with confirmed central nervous system (CNS) disease (together with either pulmonary or sinus involvement). A similar distribution of patients had IA confirmed via serologic means (36%), microbiologic (culture) means (36%), or histopathologic means (28%).

TABLE 2
Distribution of Patients by Type and Duration of Prior Antifungal Treatment

Treatment reason	Reason for study entry	
	Refractory*	Intolerant
Prior antifungal treatment	No. (%)	No. (%)
Total	46 (87)	7 (13)
Type of antifungal therapy		
Amphotericin B	4 (9)	5 (71)
Lipid amphotericin B	7 (15)	1 (14)
Itraconazole	2 (4)	0 (0)
Voriconazole	20 (43)	1 (14)
Caspofungin	4 (9)	0 (0)
>1 AntifungalM†	9 (20)	0 (0)
Duration of prior therapy		
≤14 Days	24 (52)	6 (86)
15–21 Days	11 (24)	1 (14)
22–28 Days	2 (4)	0 (0)
>28 Days	9 (20)	0 (0)

* Includes patients who were both refractory and intolerant. All 46 refractory patients received prior antifungal therapy at the predefined therapeutic doses.

† Includes combination and sequential treatment. Among these 9 patients were 7 patients who were refractory to voriconazole.

Reason for Enrollment (Refractory or Intolerant)

Forty-six (87%) patients were refractory to standard antifungal therapy (Table 1). Seven of the 46 refractory patients (15%) were also intolerant of ≥1 prior antifungal agent; however, for analysis purposes all of these patients were grouped within the refractory category. Twenty-eight of the 46 (61%) refractory patients had disease progression while on the prior therapy; the other 18 failed to show improvement on the prior regimen(s). Of note, 48% of these refractory patients received >14 days of antifungal therapy before study entry and 24% received >21 days of prior therapy. Approximately 20% of patients were refractory to multiple antifungal agents (Table 2). In the patients who were refractory to only a single prior agent, the most common prior antifungal agents, in order of decreasing use, were voriconazole, lipid amphotericin formulations, amphotericin B, and caspofungin. In general, patients who received caspofungin with an amphotericin B deoxycholate were most likely refractory to prior therapy with a polyene. Similarly, patients who received caspofungin

TABLE 3
Efficacy Outcome at the End of Combination Therapy and the Day 84 Visit

	Favorable response		
Efficacy timepoint	n/m*	(%)	95% CI
End of combination therapy	29/53	(55)	(40.4, 68.4)
Complete response	4		
Partial response	25		
Day 84 visit	25/51	(49)	(34.8, 63.4)
Complete response	7		
Partial response	18		

CI indicates confidence interval.

* n/m is the number of patients with favorable response/number of patients included in the timepoint.

with voriconazole tended to be refractory to prior therapy with voriconazole. As predefined in the protocol, all refractory patients received prior antifungals at therapeutic doses licensed for use in IA.

Seven (13%) patients were enrolled because of intolerance. All but 1 patient received $\leq$14 days of prior therapy. Only 1 patient had improvement during the prestudy period, and this patient (who received 15 days of amphotericin B deoxycholate) still had extensive disease at enrollment.

Combination Therapy Duration

The average duration of combination therapy was 31.3 days (median, 25 days; range, 1–196 days). The mean duration of exposure to combination therapy was relatively similar in patients receiving caspofungin with itraconazole (33.7 days) and patients receiving caspofungin with voriconazole (38.6 days). The extent of combination therapy was lower in patients receiving caspofungin with an amphotericin formulation (mean 16.6 days).

Overall Efficacy

Twenty-nine of the 53 (55%) patients had a favorable response at the end of combination therapy (Table 3). Of the 29 patients with a favorable response, 4 showed a complete response and 25 had a partial response. Approximately 60% of these 29 patients had noticeable improvement in clinical signs or symptoms of *Aspergillus* infection during the first 4 weeks of the study. In the 24 (45%) patients with unfavorable responses, 22 (92%) were assessed as failures and 2 (8%) were assessed as having stable disease. In fact, all patients who died while on combination therapy or during the immediate posttherapy period were assessed as failures. In those 41 patients who received >7 days of combination therapy, 66% (27/41) had a favorable response at the primary efficacy endpoint (the end of combination therapy).

TABLE 4
Overall Efficacy by Combination Treatment Regimen

	Caspofungin and amphotericin B formulation	Caspofungin and Triazoles
	N = 16	N = 37
	n/m* (%)	n/m (%)
	(95% CI)	(95% CI)
End of combination therapy		
Success	8/16 (50)	21/37† (56.8)
	(24.7, 75.3)	(39.5, 72.9)
Day 84 visit		
Success	8/16 (50)	17/35‡ (48.6)
	(24.7, 75.3)	(31.4, 66.0)

CI indicates confidence interval.

* n/m is the number of patients with favorable response/number of patients included in the timepoint

† Success for each individual regimen at the end of combination therapy: 43% (3 of 7) for caspofungin-itraconazole and 60% (18 of 30) for the caspofungin-voriconazole.

‡ Success for each individual regimen at the Day 84 visit: 29% (2 of 7) for caspofungin-itraconazole and 54% (15 of 28) for the caspofungin-voriconazole.

Two patients were not included in the efficacy assessment at Day 84 after initiation of combination therapy; both patients manifested favorable responses at the end of combination therapy but were not available for subsequent evaluation (Table 3). The proportion of patients with a favorable response at Day 84 was 49%. Included among the favorable responses at this efficacy timepoint were 7 patients with a complete response and 18 patients with a partial response.

Favorable responses were also assessed by the choice of combination therapy regimen (Table 4). Success at the end of combination therapy ranged from 43% (3 of 7) for the caspofungin-itraconazole combination to 60% (18 of 30) for the caspofungin-voriconazole combination. Among the patients receiving caspofungin with a polyene, the success rates at the end of combination therapy were 80% (4 of 5), 29% (2 of 7), and 50% (2 of 4) for patients receiving amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B, respectively. Similar trends among the combination regimens were noted in the efficacy outcomes at the Day-84 visit.

Underlying Factors Influencing Efficacy Outcome

Favorable responses at the primary efficacy timepoint (end of combination therapy) were noted

TABLE 5
Patients Outcomes at End of Combination Therapy by Specific Underlying Factors

	Caspofungin and amphotericin B formulation		Caspofungin and triazoles		Overall total	
	N = 16		N = 37		N = 53	
	n/m*	%	n/m*	%	n/m*	%
Site of infection						
Pulmonary	7/12	(58)	18/31	(58)	25/43	(58)
Sinus	1/1	(100)	1/2	(50)	2/3	(67)
Disseminated/multiple sites	0/3	(0)	2/4	(50)	2/7	(29)
Refractory or intolerant						
Refractory	5/12	(42)	20/34	(59)	25/46	(54)
Intolerant	3/4	(75)	1/3	(33)	4/7	(57)
Underlying disease/risk factor						
Hematologic disorders	8/14	(57)	19/31	(61)	27/45†	(60)
Solid organ (lung) transplant	—	—	1/1	(100)	1/1	(100)
Solid (lung) tumor	0/1	(0)	—	—	0/1	(0)
Corticosteroid use	0/1	(0)	1/5	(20)	1/6	(17)
Neutropenic status (cells/mL) at study entry						
Neutropenic (ANC <500)	5/11	(46)	11/17	(65)	16/28	(57)
Nonneutropenic (ANC ≥500)	3/5	(60)	10/20	(50)	13/25	(52)

ANC indicates absolute neutrophil count.

* n/m is the number of patients with favorable response/number of patients in the subgroup.

† Includes success in 20 (74%) of 27 patients with acute leukemia, 2 (50%) of 4 with chronic leukemia, 2 (33%) of 6 with lymphoma, and 3 (38%) of 8 with other hematologic conditions.

across a range of factors, including site of infection, reason for study entry, underlying disease, and neutropenic status (Table 5). Fifty-four percent of the patients who were refractory to prior regimens and 57% who were neutropenic at study entry had a favorable response. Higher efficacy outcomes at the end of combination therapy were noted in those patients who recovered from their neutropenia (11 of 16, 69%) as compared with those who remained neutropenic during the treatment course (5 of 12, 42%). Furthermore, 7 (54%) of the 13 patients with an allogeneic HSCT had a favorable response at the end of combination therapy. Finally, it is noteworthy that both patients with CNS infection received voriconazole in combination with caspofungin after initially progressing on prior antifungal therapy (including voriconazole monotherapy); 1 of these 2 patients responded favorably at the end of combination therapy.

Approximately 67% of the patients with infections caused by *A. fumigatus* and *A. flavus* had a favorable response at the end of combination therapy. Neither of the 2 patients with infections caused by *A. niger* responded favorably, but the 1 patient with an infection caused by *A. terreus* was successfully treated with combination therapy. In general, all isolates had low minimum inhibitory concentration (MIC) values against the 4 tested antifungals (caspofungin, amphotericin B deoxycholate, itraconazole, and voriconazole; data not shown).

Outcomes in the 46 refractory patients were also assessed at the end of combination therapy based on the treatment strategy approach. The addition of caspofungin to the initially refractory antifungal agent resulted in favorable responses in 66% (19 of 29) of the patients, whereas success was noted in 42% (5 of 12) of those patients who had caspofungin administered with a new antifungal agent. In the 5 patients who were refractory to caspofungin in the immediate prestudy period, the addition of a nonechinocandin antifungal to caspofungin resulted in a successful outcome in 1 of 5 (20%) patients. Notably, among these 46 refractory cases were 27 patients who were receiving voriconazole immediately before the onset of combination therapy. Sixteen (73%) of the 22 patients who had failed voriconazole therapy in the immediate prestudy period and subsequently had caspofungin added to voriconazole responded favorably to this combination therapy. Conversely, only 2 (40%) of the 5 patients who had discontinued voriconazole immediately before the onset of combination ther-

apy (ie, were switched to 2 new agents) responded to the subsequent combination regimen.

Mortality

Twenty-four (45%) patients died during the first 84 days of the study. Twelve deaths occurred within the first 2 weeks, and another 7 deaths occurred before Day 30. Thirteen deaths were directly related to IA progression or from related respiratory complications. The remaining deaths were the result of progression of underlying malignancies or malignant complications (4), neurologic or cardiac complications (3), multiorgan failure (2), or bacterial sepsis (2). In general, the proportion of patients who died by Day 84 were similar among the 3 treatment regimens. None of the deaths was attributed to combination therapy.

IA Recurrence

All patients with a favorable response at the Day 84 visit were followed out to 1 year posttherapy. Among these 25 patients, 4 (16%) had IA recurrence. All recurrences occurred in the setting of a worsening malignancy or increasing immunosuppression. All occurred >30 days after the end of study therapy (mean, 71 days [range = 32–167 days]). Among the 4 recurrences, 2 occurred in patients receiving suppressive antifungal therapy.

Safety and Tolerability

Among the 53 patients enrolled in the study, 52 (98%) developed at least 1 adverse event. However, drug-related clinical adverse events occurred in 32% (17/53) of patients. Drug-related clinical adverse events reported in >1 patient included hyperbilirubinemia/jaundice (9%), vomiting (6%), chills (6%), diarrhea (4%), and nausea (4%). Similarly, drug-related laboratory adverse events occurred in 21% (11/53) of patients. Drug-related laboratory events reported in >1 patient included increased serum alkaline phosphatase (11.3%), increased total bilirubin (9%), decreased serum potassium (8%), increased creatinine (6%), and increased ALT (4%). All cases of decreased potassium and increased creatinine occurred in patients receiving a polyene.

Of the 32 patients with serious adverse events, 2 patients had serious adverse events (hypernatremia; hyperbilirubinemia) reported by investigators as drug-related. Neither event was considered an unanticipated finding; both events occurred in patients receiving a caspofungin-voriconazole regimen, and both were attributed by the investigator to voriconazole. Notably, none of the patients discontinued caspofungin due to drug-related toxicity.

DISCUSSION

As monotherapy for IA is still associated with frequent failures, a strategy of employing combination therapy for the treatment of IA, particularly in the salvage setting, has become a major interest for the field of medical mycology. Herein we report the results of a multicenter study of caspofungin in combination with other antifungals in the salvage treatment of IA. To our knowledge, the current study is the first prospective trial to document the efficacy and safety of an echinocandin with other antifungal classes for the treatment of this mold infection.

As the study employed a noncomparative design, an effort was made to ensure stringent inclusion criteria and rigid definitions for favorable efficacy assessments were employed. Diagnoses of IA were based on the criteria set forth by the EORTC and BAMSG,[2] and favorable outcomes required documented resolution or significant improvement in all clinical and radiographic findings. Outcomes were assessed both at the end of combination therapy and at a defined timepoint (Day 84) after the initiation of combination therapy. Additionally, all favorable responses at these timepoints were followed for 1 year after the completion of combination therapy to assess the durability of the response. To ensure consistency in interpretation of these criteria, an independent expert assessed the accuracy of the IA diagnosis, reason for entry, and the therapeutic response at the 2 predefined timepoints.

Overall, the 53 patients included in this study represented an ill patient population with a high prevalence of poor prognostic factors. The vast majority of patients (87%) were refractory to the prior antifungal regimen, and over half the patients (53%) were neutropenic at study onset. Combination therapy resulted in a successful outcome in 55% of the patients at the end of combination therapy and in 49% of the patients at Day 84. The efficacy response was consistent across a range of factors; in fact, the majority of the patients with poor prognostic indicators, including known refractoriness to prior therapy (54%), neutropenia at study entry (57%), and the presence of an allogeneic HSCT (54%), responded favorably to combination therapy. As expected, most patients had manifested a partial, as opposed to complete, response to the combination regimen. A complete response was difficult to achieve as it mandated a completely normal follow-up radiograph. Despite the high incidence of partial responses, the occurrence of IA recurrence over the 1 year posttherapy observation period was relatively low. Finally, it is noteworthy that 55% of the patients were still alive at the Day 84 visit.

Although the study allowed for the enrollment of a number of potential combination regimens, any

numerical differences among the various regimens should be viewed cautiously. Patients enrolled in the study were not stratified based on prognostic factors, and the chosen combination therapy regimen was not randomized. The potential for selection bias regarding the choice of combination therapy must be acknowledged, as the underlying severity of a particular patient's condition may have ultimately impacted the selection of the combination therapy regimen. The small number of patients receiving each combination therapy regimen and the differences in sample sizes among the 2 treatment regimens must also be considered. Notwithstanding, it is noteworthy that the proportion of patients with a favorable response at the end of combination therapy and Day 84 visit were numerically greater among the caspofungin-voriconazole (54%) and caspofungin-polyene (50%) regimens, as compared with the caspofungin-itraconazole (29%) regimen. However, the proportion of patients who had died by the Day 84 visit was similar among the different treatment regimens.

Inherent limitations in comparing the efficacy results in this study to published data on the use of monotherapy for the salvage treatment of IA must also be acknowledged. The current study was conducted at a time separate from prior monotherapy studies. As a result, the diagnostic definitions of IA, the choice of initial antifungal agents, and the dose of study therapy employed for the current study differed from prior salvage monotherapy studies.[7,9,11] Furthermore, the studies varied in the distribution of patients with specific prognostic factors. However, despite these caveats, a review of the response at the end of caspofungin therapy from the current study to the response at the end of caspofungin study therapy in the prior caspofungin salvage monotherapy study[9] failed to demonstrate statistically significant improvement of combination therapy as compared with caspofungin monotherapy, as there was notable overlap in the 95% CI for both the overall response and specific patient subsets.

Combination therapy was well tolerated. Only 2 (4%) serious adverse events were considered by the investigator as related to study therapy; neither was an unanticipated finding, and both were attributed to the voriconazole component. Most drug-related events were of mild intensity and few resulted in discontinuation of any component of the combination regimen. No concerning pattern was identified among these therapy-related events—many events occurred in only 1 or 2 patients each. None of the 53 patients enrolled had caspofungin discontinued as a result of toxicity. Significant hepatotoxicity and nephrotoxicity were also not seen.

In summary, combination therapy involving caspofungin and other antifungal agents was effective and generally well tolerated as salvage therapy in patients with IA. Combination therapy was associated with favorable outcomes in many patients with an expected poor prognosis. Although no firm conclusions for the use of combination therapy relative to monotherapy can be drawn based on the efficacy results of this study, the outcomes with combination therapy are likely no worse than those previously reported with monotherapy regimens. Furthermore, the variety of combination therapy regimens employed in this study appeared to be well tolerated. A randomized, comparative study of monotherapy versus combination therapy, especially in the primary setting, is needed to definitely determine both the scientific and economic value of this therapeutic strategy.

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