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Salvage therapy with caspofungin for invasive aspergillosis: results from the caspofungin compassionate use study

Nicholas A. Kartsonis*, Alfred J. Saah, C. Joy Lipka, Arlene F. Taylor, Carole A. Sable

Merck Research Laboratories, Merck and Co., Inc., BL 3-4, PO Box 4, West Point, PA 19486-0004, USA

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Summary *Objectives*. The objective was to prospectively assess the efficacy and safety of caspofungin as salvage therapy for invasive aspergillosis in patients enrolled in the caspofungin compassionate-use study.

Methods. Forty-eight patients with invasive *Aspergillus* infections (36 with pulmonary infection, 12 with extrapulmonary or disseminated infection) were enrolled in this study. All patients were refractory to or intolerant of intravenous amphotericin B or a lipid amphotericin formulation(s). Efficacy was assessed at end of intravenous caspofungin therapy based on the clinical (symptom/sign and radiographic) response.

Results. Underlying diseases included hematological malignancy (69%), organ transplant (8%), and AIDS (6%). Forty-three (90%) patients were refractory to prior antifungal treatment, including 25 patients refractory to multiple agents. Sixteen (33%) were neutropenic at study entry. Following caspofungin therapy, a favorable response was noted in 44% (20/45) of the patients, including nine (20%) and 11 (24%) patients with complete and partial responses, respectively. Caspofungin was generally well tolerated one serious drug-related adverse event was reported.

Conclusions. In this study, caspofungin was an effective alternative for patients with refractory *Aspergillus* infections.

Introduction

The incidence of invasive fungal infections has risen dramatically in the last two decades, due in large part to an increased number of immunocompromised patients and the increased use of invasive procedures.[1] In fact, *Aspergillus* is now the second most common fungal pathogen encountered in the hospital setting, accounting for approximately 30% of the fungal infections in cancer patients.[2–5] Unfortunately, despite antifungal treatment, the crude mortality rate of invasive aspergillosis (IA) infections still remains unacceptably high, approaching 90% in the most severely immunocompromised hosts.[6]

Diagnostic difficulties contribute, in part, to the high mortality seen with IA.[7] Shortcomings with the currently available antifungal arsenal against *Aspergillus* species also contribute to the high

*Corresponding author. Tel.: +1-484-344-7301; fax: +1-484-344-3370.
E-mail address: nicholas_kartsonis@merck.com

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mortality rate. Amphotericin B deoxycholate, a polyene antifungal, has long served as the mainstay for the treatment of IA on account of its long-standing use and its known fungicidal action; however, several recent IA studies indicate that the overall response rate of primary treatment is low (less than 40%) and even lower for certain high-risk treatment groups.[8-10] Dose-limiting nephrotoxicity, acute infusion-related toxicity, and electrolyte imbalances further limit its use. The lipid formulations of amphotericin B, including the liposomal, lipid complex, and colloidal dispersion formulations, are associated with less toxicity[11-15] and an improved therapeutic index of amphotericin B;[16] however, these lipid-based delivery systems have not yet been proven to offer an efficacy benefit relative to conventional amphotericin.[14,16-18]

The antifungal triazoles, itraconazole and voriconazole, comprise a second class of compounds approved for treatment of IA.[19-23] In fact, recent results suggest a potential efficacy benefit with voriconazole, relative to amphotericin B, for the first-line treatment of IA; however, despite its benefit, only about 50% of the patients within the voriconazole treatment arm responded favorably.[19] Azole use is also not without its own limitations; treatment with either itraconazole or voriconazole may be hampered by drug-related toxicity, significant drug interactions, or other pharmacokinetic obstacles.

There remains a significant medical need for newer classes of antifungal agents to combat invasive *Aspergillus* infections. Unlike the currently available agents, caspofungin (formerly MK-0991, L-743,872), the first approved agent from the echinocandin class of antifungals, inhibits fungal cell wall glucan synthesis. Caspofungin has demonstrated activity both in vitro and in vivo, against *Aspergillus* species.[24-28] Animal models which incorporate molecular techniques to quantitatively measure fungal burden (PCR) note a significant count reduction in *Aspergillus* in target organs and improved survival following caspofungin therapy.[29] Because of its unique mechanism of action, cross-resistance with conventional antifungal compounds, which primarily target the fungal cell membrane, is not anticipated.[30-34] In fact, the results from an initial monotherapy trial demonstrated a 45% favorable outcome rate with caspofungin for the salvage treatment of IA and led to the licensure of caspofungin for this indication.[35] Herein we report additional data from a prospective compassionate use study, wherein 48 patients with documented IA received caspofungin as salvage therapy.

Patients and methods

Study population

The caspofungin compassionate use study (Merck MX-0991 Protocol 024/025), a worldwide patient-named trial, was conducted prior to the licensure of caspofungin. Enrollment was open to patients with either a documented *Aspergillus* or *Candida* infection in those countries whose regulatory agencies approved the protocol and no other mechanism was in place to allow patients to receive caspofungin.

Inclusion in the *Aspergillus* portion of the study required that adult patients, between the ages 18 and 80 years, to have either definite or probable aspergillosis. The definitions of disease were modeled after the Mycosis Study Group criteria for invasive aspergillosis.[36] Definite disease was defined as the presence of either (1) tissue histopathology with evidence of invasive *Aspergillus* infection or (2) a positive culture for *Aspergillus* species from tissue obtained by an invasive procedure (e.g., open lung biopsy, transbronchial biopsy, percutaneous needle aspiration). For this study, probable disease signified radiographic evidence of disease and either (1) a positive culture for *Aspergillus* species from either sputum or bronchoalveolar lavage (BAL) or (2) two or more consecutively positive results for *Aspergillus* on plasma galactomannan enzyme-linked immunosorbent assay (ELISA). Patients lacking histopathological, microbiological, or serological evidence suggestive of IA were not eligible for enrollment. All patients were either refractory to or intolerant of standard therapy with an intravenous amphotericin formulation. Refractory was defined as clinical or microbiological progression of disease or lack of improvement despite at least 7 days of therapy with an intravenous amphotericin formulation (IV amphotericin B deoxycholate, liposomal amphotericin B [AmBisome®, Fujisawa, USA], amphotericin B lipid complex [ABELCET®, Enzon Pharmaceuticals, USA], or amphotericin B colloidal dispension [AMPHOTEC®, Sequus Pharmaceuticals, USA]. Intolerance included patients with a serum creatinine increase to $\geq$2.5 mg/dL or other significant intolerance while receiving amphotericin B or its lipid formulations (e.g., acute, severe infusion-related toxicity). All women of childbearing potential had a negative pregnancy test for human chorionic gonadotropin (HCG) prior to enrollment into the study.

Exclusion criteria included a prior history of allergy or serious reaction to echinocandins or known acute hepatitis or cirrhosis (of any cause).

Ongoing treatment with cyclosporin A or other concomitant systemic antifungal agents was also not allowed, unless a prior approval had been issued by the Merck monitor physician. Abnormal laboratory values that disqualified patients from study participation were hemoglobin of <7 gm/dL, platelet count of $<50{,}000\ \mu L^{-1}$ for non-neutropenic patients ($<5000\ \mu L^{-1}$ for neutropenic patients), total serum levels of bilirubin three or more times the upper limit of normal (ULN), levels of serum transaminases or serum alkaline phosphatase of five or more times the ULN, or an international normalization ratio (INR) of >3 in patients not receiving anticoagulant therapy. Patients with allergic bronchopulmonary aspergillosis were excluded. Similarly, patients with aspergilloma or ocular disease were also ineligible, unless appropriate surgical procedures were performed prior to study entry.

Written, informed consent was obtained from all patients or their families. The emergency use of caspofungin was acknowledged by each participating site's institutional review board.

Study design

The compassionate-use study was a non-comparative open-label, multisite trial consisting of a preliminary prescreening period, a study therapy period, and a follow-up visit 14 days following the completion of caspofungin therapy. Patients with IA who successfully fulfilled the selection criteria were treated with IV caspofungin 50 mg/day, following a 70 mg loading dose on Day 1. All caspofungin infusions were administered once daily, with each infusion lasting approximately 1 h.

The duration of treatment was individualized for each patient based on the patient's underlying disease and clinical response to therapy. In general, patients with IA were to be treated for a minimum of 28 days and a maximum of 90 days. However, therapy with caspofungin could be extended beyond 90 days on a case-by-case basis after prior discussion with the Merck physician. In general, all patients were to be treated for at least 7 days following the resolution of symptoms. Furthermore, patients with neutropenia were to be treated with caspofungin for at least 14 days after the resolution of the neutropenia (until absolute neutrophil count, or ANC, was greater than $500\ \mu L^{-1}$); shorter courses may have been given to those patients in whom neutropenic resolution was not anticipated.

Patients were evaluated on a weekly basis while receiving caspofungin therapy. Modification of study dosing was not permitted, but therapy could be temporarily interrupted. Following cessation of therapy, all patients were to be reevaluated 14 days following the cessation of caspofungin.

The protocol also allowed for potential retreatment courses with caspofungin. Patients were retreated for recurrences or other justifiable conditions only after discussion with the Merck physician. Patients could be retreated a maximum of three times.

Efficacy and safety evaluations

An assessment of signs and symptoms of infection was made in each patient on a weekly basis during IV therapy; however, the primary assessment of response in each patient was performed by the investigator at the end of caspofungin therapy. A favorable response included assessments of either 'complete response' or 'partial response.' A complete response mandated the resolution of all symptoms or signs, radiographic findings, and bronchoscopic abnormalities attributable to the *Aspergillus* infection. A partial response was defined as clinically meaningful improvement of the clinical symptoms and signs of infection and relevant improvement of radiographic and bronchoscopic abnormalities due to the *Aspergillus* infection. Unfavorable responses at the end of caspofungin therapy included any patient who did not meet the definition of a favorable response (patients with documented 'failure' or 'stable disease').

The safety of IV caspofungin was evaluated by determining the presence of adverse events. On a daily basis during the IV caspofungin therapy period, the investigator monitored each patient for adverse events from both routine clinical evaluations and laboratory tests. Patients were also monitored for adverse events in the follow-up period for at least 14 days following the last dose of caspofungin. Serious clinical and laboratory adverse events and selected non-serious clinical and laboratory adverse experiences (including all drug-related adverse events) were reported to Merck.

Statistical analysis and approaches

This compassionate-use study was an open-label, non-comparative trial; no hypothesis for efficacy were predefined for this study. The primary evaluation for efficacy was the proportion of patients with a favorable outcome (complete or partial response) at the end of IV caspofungin therapy. Patients included in the efficacy evaluation represented all patients who had a proper diagnosis of infection, received at least one dose of

caspofungin, and had a clinical assessment performed by the investigator at the end of caspofungin therapy. The efficacy proportions are displayed with 95% Clopper–Pearson exact confidence intervals, based on the binomial distribution.

No statistical hypotheses were predefined for safety evaluations. All patients who received at least one dose of caspofungin are included in the evaluation of safety.

Results

Baseline characteristics of the patients

The caspofungin compassionate use trial was conducted worldwide between September 1999 and September 2002. Forty-one investigators from five different countries (United States,[21] Belgium,[9] Italy,[8] Greece,[2] and Israel[1]) enrolled a total of 48 patients with IA. The majority (69%) of the patients had hematological malignancies or other hematological disorders at study entry (Table 1). Approximately a third of these patients were recipients of either an autologous (3) or allogeneic (8) hematopoietic stem cell transplantation (HSCT). Other less common risk factors included solid organ transplantation (8%) and AIDS (6%). Two patients did not have a discernible risk factor for *Aspergillus* infection; both patients had confirmed definite disease. Neutropenia (ANC $<500\,\mu L^{-1}$) was a noted risk factor in one-third of the patients.

Table 1 Baseline demographics

Characteristic	All patients ($N = 48$)
Gender	
Male	28 (58.3)
Female	20 (41.7)
Median age, in years (range)	51 (7–89)[a]
Race	
Caucasian	41 (85.4)
Black	3 (6.3)
Hispanic	2 (4.2)
Other	2 (4.2)
Neutropenia status at study entry	
Neutropenic (ANC $\leq 500/\mu L$)	16 (33.3)
Non-neutropenic	32 (66.7)
Underlying disease	
Hematological malignancy/disorder	33[b] (68.8)
Acute leukemia	15[c]
Chronic leukemia	5[d]
Non-Hodgkin's or other lymphomas	5
Multiple myeloma	3
Myelodysplastic syndrome	2
Aplastic anemia	3
Organ transplant	4[e] (8.3)
AIDS	3 (6.3)
Other	8[f] (16.7)
Underlying site of *Aspergillus* infection	
Pulmonary	36 (75.0)
Definite	16
Probable	20
Extrapulmonary	12 (25.0)
Sinus	3
Skin	3
Disseminated	2
Other	4[g]

Data are no. (%) unless otherwise indicated.
[a] The age limits for the 7- and 89-year-olds were waived by the Monitor to allow for enrollment.
[b] Eleven of the patients had received a hematopoietic stem cell transplant for their underlying hematological condition; eight were recipients of an allogeneic transplantations.
[c] Includes eight patients with acute myelogenous leukemia, six with acute lymphoblastic leukemia, and one with acute biphenotypic leukemia.
[d] Includes three patients with chronic myelogenous leukemia and two with chronic lymphoblastic leukemia.
[e] One patient each with a lung, liver, kidney, and heart/lung transplant.
[f] Immunosuppressive therapy in two patients, trauma related to surgery in two patients, prior *Aspergillus* pneumonia in one patient, and known PPD positive status in one patient; two other patients with no identifiable risk factor.
[g] Includes one patient each with infection of the liver, lymphatic system, CNS, and spine (osteomyelitis).

Site of *Aspergillus* infection

Overall, 36 (75%) patients had pulmonary disease, including 16 definite and 20 probable cases (Table 1). Skin and sinus were the most common extrapulmonary sites of infection. Two patients (one with an infection of the lung and skin, the other of lung and CNS) had disseminated disease, defined as *Aspergillus* infection at two or more non-contiguous sites of infection (Table 1).

Reason for enrollment (refractory or intolerant)

Forty-three (90%) of the 48 patients with IA were refractory to at least one prior antifungal agent (Table 2). Of the refractory patients, 25 (58%) had failed therapy with more than one antifungal agent (including 17 who had failed both polyene and triazole therapy and eight who had failed therapy with more than one IV amphotericin preparation). An additional six (14%) patients were refractory to itraconazole only after confirmed intolerance to one or more of the polyenes. Thirty (70%) of the 43 refractory patients had manifested disease progression while on the prior therapy; the other 13

Table 2 Distribution of patients by reason of study entry and type of prior therapy

Reason for enrollment	Site of infection		Overall
Prior antifungal regimen	Pulmonary ($N = 36$)	Extrapulmonary ($N = 12$)	($N = 48$)
Refractory[a]	32 (88.9)	11 (91.7)	43 (89.6)
Amphotericin B deoxycholate	3	0	3
Lipid formulation of amphotericin B (any IV preparation)	5	4	9
Itraconazole[b]	5	1	6
Multiple agents	19[c]	6[d]	25
Intolerant	4 (11.1)	1 (8.3)	5 (10.4)
Amphotericin B deoxycholate	2	1	3
Lipid formulation of amphotericin B (any IV preparation)	1	0	1
Multiple agents	1	0	1

[a] Includes patients who may have been both refractory and intolerant of prior antifungal therapy.
[b] All six patients refractory to itraconazole were also intolerant of one or more IV preparations of amphotericin.
[c] Includes 13 patients who were refractory to both an IV amphotericin agent(s) and a triazole(s). Six other patients were refractory to more than one IV preparation of amphotericin B.
[d] Includes four patients who were refractory to both an IV amphotericin agent(s) and a triazole(s). Two other patients were refractory to more than one IV preparation of amphotericin B.

failed to show any meaningful improvement on the prior regimen(s).

Duration of caspofungin therapy

Caspofungin was administered for a mean duration of 38.3 days (range 1–129 days). Overall, a total of 23 (48%) patients received greater than 28 days of caspofungin therapy, including five who were granted permission to receive over 90 days of therapy. All but one patient received caspofungin at the 50 mg daily dose (following the 70 mg loading dose on Day 1); the one exception, a 7-year-old patient, was administered caspofungin at 1 mg/kg/day (23 mg/day).

Overall efficacy

Three (6%) of the 48 patients enrolled in this study were not evaluated for efficacy at the end of caspofungin therapy. A favorable response at the end of caspofungin therapy was noted in 20 (44%) of the 45 patients included in the efficacy analyses. Complete and partial responses were noted in nine (20%) and 11 (24%) patients, respectively (Table 3). Of the 25 patients who had an unfavorable response, 20 were considered failures and the other five were classified as having stable disease at the end of caspofungin.

Efficacy by significant underlying factors

The proportion of patients with a favorable response is displayed by a number of clinically relevant baseline factors, such as underlying disease and site of infection, in Table 4. In general, favorable responses were noted across all the different subgroups. Higher success rates were noted in patients with non-hematological diseases (nine of 15, or 60%) than patients with hematological conditions (11 of 37, or 37%). Patients with pulmonary infections (18 of 34, or 53%) fared, better than patients with extrapulmonary infections (two of 11, or 18%). As expected, the eight patients who had received an allogeneic transplant had the poorest outcome.

Neutropenia is another significant prognostic factor in patients with IA. Approximately 30% of the patients with neutropenia at study entry had a favorable response to caspofungin (Table 4). Notably, two of these neutropenic patients and one other patient who became neutropenic during the treatment course as a result of consolidative chemotherapy responded successfully to caspofungin even

Table 3 Favorable outcomes at the end of caspofungin therapy

Assessment time point	Complete response n/m[a] (%) (95% CI)[b]	Partial response n/m (%) (95% CI)	Overall favorable response n/m (%) (95% CI)
End of caspofungin therapy	9/45 (20.0) (9.6, 34.6)	11/45 (24.4) (12.9, 39.5)	20/45 (44.4) (29.6, 60.0)

[a] This signifies the number of patients with a favorable response/the number of assessable patients included in the infection group.
[b] Represent the 95% Clopper–Pearson exact confidence intervals, based on the binomial distribution.

Table 4 Efficacy based on underlying factors

Subgroup	Favorable outcome to caspofungin	
	n/*m*[a]	(%)
Underlying disease		
Hematological malignancy/disorder	11/30[b]	(36.7)
Organ transplant		(25.0)
AIDS	3/3	(100.0)
Other	5/8	(62.5)
Site of infection		
Pulmonary	18/34	(52.9)
Definite	8/16	
Probable	10/18	
Extrapulmonary	2/11	(18.1)
Sinus	0/2	
Skin	1/3	
Disseminated	0/2	
Other	1/4[c]	
Reason for study entry		
Refractory	16/40[d]	(40.0)
Intolerant	4/5	(80.0)
Neutropenic status		
Neutropenic (ANC $\leq 500/\mu L$)	4/13	(30.8)
Non-neutropenic	16/32	(50.0)
Pathogen[e]		
A. fumigatus	9/20	(45.0)
A. flavus	0/1	(0)
A. niger	1/1	(100.0)
A. terreus	0/2	(0)
Mixed infection	1/2	(50.0)
Aspergillus not speciated or diagnosis not confirmed microbiologically	9/19	(47.4)

[a] The *n*/*m* signifies the number of patients with favorable response/number of assessable patients in that subgroup.
[b] Includes success in six (42.9%) of 14 patients with acute leukemia, one (25%) of four patients with chronic leukemia, two (50%) of four patients with lymphoma, one of three patients with multiple myeloma, one of three patients with aplastic anemia, and neither of the two patients with myelodysplastic syndrome. One (33%) of the three patients with an autologous HSCT and none of the eight patients with an allogeneic HSCT transplantation responded favorably.
[c] Includes a favorable outcome in one patient with spinal osteomyelitis. One patient with a confirmed CNS infection failed to respond to caspofungin.
[d] Includes a favorable outcome in 12 (42.9%) of the 28 patients whose infection had progressed on prior antifungal therapy and four (33.3%) of the 12 patients who had no improvement on prior therapy.
[e] Information on *Aspergillus* species was obtained from the case report form and was based solely on data from the microbiology laboratory. Data on susceptibility pattern was not collected.

though all three patients were still identified as neutropenic at the end of study therapy.

Outcome was also assessed based on the reason for study entry and the type of prior therapy. Sixteen (40%) of the 40 patients who were refractory to at least one prior antifungal agent, including 12 (43%) of the 28 patients with disease progression on the prior regimen(s), responded favorably (Table 4). Of note, six (27%) of the 22 patients who were refractory to multiple antifungal agents prior to study onset were categorized as having a favorable response to caspofungin. Four (67%) of the six patients who were both refractory to itraconazole and intolerant of an IV amphotericin preparation were also deemed caspofungin successes. In contrast, four (80%) of the five patients who were intolerant of a polyene prior to study entry exhibited a favorable response at the end of caspofungin therapy.

Mortality

A total of 24 (50%) patients died either during the course of study therapy or in the follow-up period. The majority of the deaths (19, or 79%) were directly related to progression of the aspergillosis or from related respiratory complications; each occurred while the patient was receiving caspofungin or in the few days following its discontinuation. All of these patients were considered efficacy failures. The remaining five deaths were the result of progression of hematologic malignancies or other malignant complications (e.g., pancytopenia-induced intracranial hemorrhage). None of the deaths was attributed to caspofungin therapy.

Combination therapy

Ten (21%) of the 48 patients with IA received caspofungin in combination with another antifungal agent during the course of the study. Each of these 10 patients was deemed by the respective investigator at the time of enrollment as too ill to warrant monotherapy; thus, given the protocol's compassionate use nature, the use of caspofungin with other concomitant antifungal agents was permitted. Multiple poor prognostic factors were noted in this group at baseline: seven of the 10 patients had definite aspergillosis (four with extrapulmonary disease), nine had an underlying hematological malignancy (four allogeneic HSCT recipients), and five were neutropenic. All 10 patients were refractory to at least one prior antifungal agent, including seven patients who were refractory to more than one antifungal agent in the prestudy period. In all 10 cases, the patient was also refractory to the antifungal agent used in combination with caspofungin.

The most common agent used in combination with caspofungin was liposomal amphotericin (5), followed by amphotericin lipid complex (8),

itraconazole (1), and the combination of liposomal amphotericin and itraconazole (1). Duration of combination therapy ranged between 2 and 82 days (mean 25 days, median 16 days). A favorable response at the end of caspofungin therapy was noted in one (10%) of the 10 patients. The one success was the single patient who received caspofungin in combination with itraconazole. Seven (70%) of the 10 patients died while on combination therapy or in the immediate follow-up period; all but one death was related to progressive aspergillosis or other related respiratory events (cardiopulmonary arrest, respiratory failure, or alveolar hemorrhage).

Safety and tolerability

Of the 48 patients enrolled with IA, only one (2%) serious drug-related adverse event was reported; this patient with known acute biphenotypic leukemia developed anaphylaxis to caspofungin (characterized by stridor/dyspnea, facial swelling, and accentuation of a preexisting skin rash) approximately 10 min into the infusion. All symptoms resolved within 15 min following the interruption of the caspofungin and the administration of diphenhydramine and hydrocortisone. Four other patients (8%) developed non-serious, drug-related adverse events: diarrhea, dizziness, fever, and hypercalcemia in one patent each. Only the one patient with anaphylaxis was discontinued for a drug-related adverse event.

Antifungal therapy was well tolerated in the subset of patients who received caspofungin in combination with other antifungal agents. None of these 10 patients developed a drug-related adverse experience during the treatment course, despite receiving combination therapy for a mean of 24.6 days (median, 16 days; range, 2–82 days).

Discussion

In 1999, prior to the licensure of caspofungin (CANCIDAS®), we initiated a compassionate use study to provide this echinocandin antifungal agent to those patients who warranted alternative antifungal therapy but who were hospitalized at medical centers not participating in caspofungin clinical trials. Herein we provide the results from the *Aspergillus* portion of this study. To our knowledge, this study represents only the second trial to prospectively evaluate caspofungin monotherapy as a second-line treatment option for patients with IA. Stringent inclusion criteria were implemented for this study. The definitions of disease were modeled after Mycoses Study Group Criteria;[36] enrollment was strictly limited to patients with either definite or probable cases of IA. Eligible patients had to also satisfy the standardized definitions of refractoriness or intolerance to prior antifungal therapy before enrollment could be considered.

As expected, the most prevalent risk factor in these patients enrolled with IA was an active hematologic malignancy or other active hematologic process. Approximately one quarter of the patients were recipients of either an allogeneic or autologous HSCT, and one third were neutropenic at study onset. Although the trial required that patients be either refractory to or intolerant of amphotericin B or a lipid amphotericin preparation, 90% of the enrolled patients with invasive *Aspergillus* infections were actually refractory to one or more antifungal agents. In fact, the majority (58%) of these patients were refractory to multiple prior therapies, with 17 (35%) of 48 having failed prior treatment with at least one polyene and one azole, either as sequential or combination therapy. Overall, caspofungin was an effective option for these patients with IA, with successful outcomes achieved in approximately 45% of the cases. Responses were noted across diverse sites of infection, in patients with varying underlying diseases, and in both the neutropenic and non-neutropenic setting. In the setting of extended treatment courses (mean 38.3 days, range 1–129 days), caspofungin therapy remained generally well tolerated with a low frequency of drug-related adverse events and drug-related discontinuations.

Overall, the results of this study closely mirror the findings of the initial caspofungin salvage monotherapy trial in patients with IA.[35] Similar enrollment criteria and outcome assessments were implemented in the two studies; however, one notable distinction was the use of an independent expert panel to assess the efficacy in the original study. In both the initial study and this follow-up compassionate use study, patient demographics and baseline characteristics were similar with regard to the underlying disease (72 and 69% with hematological disorder, respectively) site of infection (77 and 75% with pulmonary aspergillosis), and reason for study entry (86 and 90% with refractory cases). Of note, outcome evaluations were also similar with success noted in 45 and 44% of the cases in the original study and the compassionate use trial, respectively. Even the outcomes in the various subgroups—patients with hematological disorders (42 and 37%), pulmonary aspergillosis (50 and 53%), refractory disease (39 and 40%), or

underlying neutropenia (26 and 31%)—were highly consistent.[35]

Both studies demonstrate that the outcome with caspofungin monotherapy in certain high-risk patients, namely prior recipients of an allogeneic HSCT, was poor, as expected.[35] A low success rate in the HSCT population reflects the ongoing need in this patient population for aggressive immunosuppressive therapy to ameliorate the effects of graft-versus-host disease.[37] Given the poor outcome in these patients with any one monotherapy regimen and the novel mode of action for caspofungin relative to the triazole and polyene agents, an argument could be made for the potential use of combination therapy in HSCT recipients. In the small subset of patients who received combination therapy in this study, such an approach was not effective; only one of the 10 patients, who received combination therapy, including none of the four allogeneic HSCT recipients, responded favorably. However, the results in this group are limited and somewhat biased in that combination therapy was only granted in those patients whom the investigator specifically requested its use. Hence, only patients with multiple poor prognostic factors were given combination therapy. As all 10 patients had caspofungin added to an antifungal agent the patient was already failing, this study does not represent an optimal assessment of combination therapy. Other studies involving combination therapy with caspofungin have reported more encouraging results, in both the primary and salvage setting.[38–42] Clearly, the issue of combination antifungal therapy warrants further evaluation before any firm conclusions may be drawn with regards to its use.

In this study, caspofungin was found to be an effective and well tolerated alternative for the salvage treatment of IA. The remarkable consistency between the efficacy data from this study and from the earlier caspofungin monotherapy trial are further testimony to its activity against this difficult-to-treat infection. The results lend further support for the use of caspofungin monotherapy in the treatment of IA, particularly in patients with infections refractory to conventional antifungal agents.

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The following investigators participated in this study: Belgium—M. Aoun (Institut Jules Bordet, Brussels), Z. Berneman (Antwerp University Hospital, Edegem), G. Bries (Virga Jesse ZH, Hasselt), R. Colebunders (University Hospital Antwerp, Edegem), H. Demuynck (Heilig Hartziekeknhuis Roeselare, Roeselare), B. DePrijck (Centre Hospitalier Regional D La Citadelle, Liege), F. Jacobs (Hôpital Université Erasme, Brussels), E.M. Veys (Universitair Zlekenhuis Gent, Gent), P. Zachee (Universitair Zlekenhuis Gasthuisberg Hospital, Leuven); Greece—J. Christakis (Anticancer Hospital of Thessaloniki, Thessaloniki), H. Giamarellou (Laiko General Hospital, Athens); Italy—T. Barbui (Ospedali Riuniti de Bergamo, Bergamo), F. DeLalla (Osperdale S. Bortolok, Vincenza), F. Lauria (Osperdale A Sclavo, Siena), A. Lazzarin (Osperdale San Rafaele, Milano), L. Pagano (Policlinico Gemelli, Roma), A. Tassara (Osperdale Regionale U.O. Malattie Infettive, Acosta), F. Vinante (Osperdalieri Di Verona, Verona), C. Viscoli (Osperdale San Martino, Genova); Israel—N. Haddad (Rambarn Medical Center, Haifa); United States—R. Adam (University of Arizona College of Medicine, Tucson, AZ), E. Atkinson (University of Wisconsin, Madison, WI), R. Betts (The University of Rochester School of Medicine and Dentistry, Rochester, NY), D. Claxton (Penn State Hershey Medical Center, Hershey, PA), L.E. Damon (University of California/Mount Zion Cancer Center, San Francisco, CA), E. Epner (Arizona Cancer Center, Tucson, AZ), A.C. Fuchs (Hahnemann University Hospital, Philadelphia, PA), M. Gottlieb (Beer Medical Group, Los Angeles, CA), L. Irizarry (Albuquerque VA Medical Center, Albuquerque, NM), M.A. Khan (Thomas Jefferson University Hospital, Philadelphia, PA), J.M. Kilby (University of Alabama at Birmingham, Birmingham, AL), J. Kurtzberg (Duke University Medical Center, Durham, NC), A.M. Levine (University of Southern California/Norris Cancer Hospital, Los Angeles, CA), R. Levitz (Hartford Hospital, Hartford, CT), C. Linker (University of California, San Francisco, CA), De Siegel (Morristown Memorial Hospital, Morristown, NJ), L. Sloan (Baylor University Medical Center, Dallas, TX), G. Sutherland (Holy Cross Hospital, Fort Lauderdale, FL), L. Teperman (New York University Medical Center, New York, NY), R. Tofte (Mercy Health Care Center, Coon Rapids, MN), Koen VanBesien (The University of Illinois at Chicago, Chicago, IL).

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