MAJOR ARTICLE

Efficacy and Safety of Caspofungin for Treatment of Invasive Aspergillosis in Patients Refractory to or Intolerant of Conventional Antifungal Therapy

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Background. Invasive aspergillosis (IA) is an important cause of morbidity and mortality among immunocompromised patients. Echinocandins are novel antifungal molecules with in vitro and in vivo activity against *Aspergillus* species.

Methods. We investigated the efficacy and safety of caspofungin in the treatment of IA. Ninety patients with IA who were refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B, or triazoles were enrolled to receive caspofungin.

Results. Efficacy was assessed for 83 patients who had infection consistent with definitions of IA and who received ⩾1 dose of study drug. Common underlying conditions included hematologic malignancy (48% of patients), allogeneic blood and marrow transplantation (25% of patients), and solid-organ transplantation (11% of patients). Seventy-one patients (86%) were refractory to and 12 patients (14%) were intolerant of previous therapy. A favorable response to caspofungin therapy was observed in 37 (45%) of 83 patients, including 32 (50%) of 64 with pulmonary aspergillosis and 3 (23%) of 13 with disseminated aspergillosis. Two patients discontinued caspofungin therapy because of drug-related adverse events. Drug-related nephrotoxicity and hepatotoxicity occurred infrequently.

Conclusion. Caspofungin demonstrated usefulness in the salvage treatment of IA.

During the past 2 decades, invasive aspergillosis (IA) has emerged worldwide as an important cause of nosocomial and community-acquired infection among a wide spectrum of immunocompromised patients [1–5], including patients undergoing cancer chemotherapy, hematopoietic stem-cell transplantation (HSCT), or solid-organ transplantation and patients with advanced HIV infection [6, 7]. Pulmonary aspergillosis has emerged as the most common attributable cause of mortality due to infectious pneumonia among bone-marrow transplant recipients. The overall mortality rate for IA remains dramatically high, approaching 90% in populations of the most profoundly immunocompromised patients [8, 9].

The therapeutic options available to treat IA are limited to a small arsenal of antifungal compounds. For the past 4 decades, deoxycholate amphotericin B has been considered to be the standard antifungal agent for treatment of IA in severely immunocompromised patients, because of its historically long record and the lack of suitable parenteral alternatives. However, the usefulness of deoxycholate amphotericin B is hampered by dose-limiting nephrotoxicity and acute infusion-related toxicity. Several recent studies have indicated that the overall response rate to treatment is <40% and may be as low as 10%–15% among patients undergoing allogeneic HSCT [7–9]. The lipid formulations of amphotericin B are associated with less toxicity at higher dosages [10–15]; however, their overall efficacy at cur-

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rent therapeutic dosages may be similar to that of deoxycholate amphotericin B in the primary treatment of IA [16].

The antifungal triazoles, itraconazole and voriconazole, constitute another class of compounds used for treatment of IA [17–21]. These compounds have the merit of being available in oral and parenteral formulations. Moreover, voriconazole is superior in efficacy to deoxycholate amphotericin B in the primary treatment of IA [17]. However, the use of triazoles may be hampered by drug-related hepatotoxicity and hazardous drug interactions.

The echinocandins are a novel class of parenterally administered semisynthetic lipopeptides with a pathogen-specific mechanism for noncompetitive inhibition of biosynthesis of 1,3-β-glucans in the fungal cell wall [22, 23]. The echinocandins have documented in vitro and in vivo activity against *Candida* and *Aspergillus* species [24–28]. The absence of a cell wall and of 1,3-β-glucan synthesis in mammalian cells is associated with a high therapeutic index for this class of compounds.

Caspofungin is the first compound of the class of echinocandins to be studied for treatment of IA in humans. Laboratory investigations have demonstrated that caspofungin is comparable in efficacy but less toxic than conventional amphotericin B in animal models of pulmonary and disseminated aspergillosis [26–29]. The excellent safety profile evident for patients with esophageal candidiasis permitted the study of caspofungin for the treatment of more-complicated infections, such as IA in immunocompromised patients [30, 31]. In this article, we report the results of the first clinical study of the use of an echinocandin in the treatment of IA.

PATIENTS AND METHODS

The study was an open, noncomparative, multicenter clinical trial designed to estimate the efficacy and safety of caspofungin therapy among patients with IA. The protocol was approved by the institutional review boards of all the participating centers. Written informed consent was obtained from all enrolled patients.

Inclusion and exclusion criteria. Patients were eligible for enrollment if (1) they had infection that met the definition of proven or probable IA, and (2) they were refractory to or intolerant of standard anti-*Aspergillus* therapy. Proven IA required histopathological evidence of tissue invasion with hyphae morphologically consistent with *Aspergillus* species (with or without a culture positive for *Aspergillus* species from the same site) or, in the absence of histopathological testing, a culture positive for *Aspergillus* of a sample that was obtained from a sterile site by an invasive procedure (e.g., percutaneous needle aspiration). For this study, the definition of probable IA applied only to pulmonary disease and required radiological and microbiological evidence of acute IA in the protocol-specified populations of immunocompromised patients, which included those with neutropenia (neutrophil count, <500 cells/μL), those who had received cytotoxic agents or corticosteroids ($\geq$10 mg prednisone or the equivalent daily), and those with inherited or acquired immunodeficiency. Probable pulmonary IA was defined by either of the following sets of criteria: (1) the appearance of new nodules or cavities on a chest radiograph, together with 2 sputum cultures positive for *Aspergillus* species or 1 positive result by direct examination or by culture of a bronchoalveolar lavage (BAL) specimen; or (2) results of a chest CT scan that were consistent with IA (i.e., "halo" or "air crescent" sign or pleural-based angular lesion), plus either a positive result by direct examination or by culture of any respiratory specimen or at least 2 consecutive positive results by galactomannan ELISA of serum or BAL samples or PCR analysis positive for *Aspergillus* from at least 2 BAL samples. The diagnosis for patients enrolled as having probable pulmonary disease was changed to proven disease on the basis of the results of a later invasive procedure or an autopsy.

Patients with proven IA or probable pulmonary IA were eligible for this study if they were refractory to or intolerant of standard therapy. The term "refractory" was defined as demonstration of progression of disease or failure to improve clinically despite receiving at least 7 days of standard therapy. Standard therapy included amphotericin B, lipid formulations of amphotericin B, or itraconazole. Patients unresponsive to therapy with investigational triazoles with anti-*Aspergillus* activity (e.g., voriconazole) also were enrolled. Intolerance of standard therapy referred to the development of nephrotoxicity (defined as doubling of baseline serum creatinine or creatinine level [>2.5 mg/dL] while receiving standard therapy), pre-existing renal impairment (serum creatinine level, >2.5 mg/dL), or any other significant intolerance to prior therapy (e.g., severe infusion-related reaction or elevated serum transaminase levels).

Exclusion criteria included a history of allergic or serious reaction to echinocandins; ongoing treatment with rifampin, ritonavir, or cyclosporin A; and any underlying condition deemed likely to confound interpretation of the results or to pose undue risk to the patient. Abnormal laboratory results that disqualified patients from participation in the study were a hemoglobin level <8 g/dL, a platelet count <25,000 cells/μL, a total serum bilirubin or alkaline phosphatase level $\geq$3 times the upper limit of normal (ULN), serum transaminase levels $\geq$5 times the ULN, or a prothrombin time greater than the ULN.

Treatment regimen and study design. A 70-mg loading dose of caspofungin was given on the first day of treatment, followed by 50 mg daily for the remainder of therapy. Caspofungin was given intravenously as a single daily dose infused over ~1 h. Duration of therapy was based on the severity of underlying disease, recovery from immunosuppression, and rapidity of clinical response. In general, patients were treated for

a minimum of 28 days and for at least 7 days after resolution of symptoms. Patients with neutropenia were treated for at least 14 days after resolution of neutropenia (neutrophil count, ⩾500 cells/μL). The protocol initially defined a maximum of 90 days of therapy, but some patients who benefited were treated longer. Patients were observed for 28 days after discontinuation of caspofungin therapy. After completion of caspofungin therapy, suppressive itraconazole therapy was given as clinically indicated and as tolerated.

Physical examination, an overall clinical assessment, and a detailed description and evaluation of the extent and severity of IA were done at baseline, twice weekly during intravenous therapy, on the last day of study therapy, and at a 4-week follow-up visit after completion of therapy with the study drug. Samples obtained by noninvasive means, such as specimens for fungal culture or serum for galactomannan ELISA or PCR, were collected at specified intervals during therapy.

Assessment of response. Each patient was assessed on the basis of data recorded on case-report forms and the official reports of radiographs, surgical procedures, bronchoscopies, and autopsies. A panel of 3 experts in medical mycology (T.J.W., D.W.D., and T.F.P.) independently evaluated the diagnosis of IA, the reason for enrollment (whether patients were refractory to or intolerant of standard therapy), and the response to caspofungin therapy. The primary assessment of clinical response was made at the end of intravenous therapy. When ⩾1 member of the expert panel disagreed with the investigator's assessment, the case was discussed at a face-to-face meeting, where radiographs and scans were reviewed when assessments were particularly complex or uncertain. The majority decision was recorded as final. These final assessments of response by the expert panel were used for all analyses in this report.

The term "favorable response" was used to denote either a complete or partial clinical response. The stringent requirements for the designation "complete response" were resolution of all clinical signs and symptoms attributable to IA and complete resolution of radiographic or bronchoscopic abnormalities. The term "partial response" denoted clinically meaningful improvement of all clinical signs and symptoms attributable to IA (usually resolution) and significant improvement of radiographic (at least 50%) or bronchoscopic abnormalities. A partial response included persistence of radiographic sequelae (e.g., persistent scar), regardless of the overall level of clinical or radiographic improvement.

Patients were considered to have an "unfavorable response" if they had stable disease or experienced therapy failure. "Stable disease" was defined as no improvement of clinical signs or symptoms attributable to IA and no improvement of radiographic or bronchoscopic abnormalities. "Failure" was defined as deterioration in clinical or radiographic abnormalities attributable to IA, necessitating alternative antifungal therapy or resulting in death. Finally, the term "relapse" indicated reemergence of IA after discontinuation of therapy, following a complete or partial response.

Because the diagnosis of IA did not always require microbiological culture for evidence of *Aspergillus* infection, the mycological outcome was evaluated separately and did not affect assessment of the primary end point of clinical response. "Eradication" signified negative culture results at follow-up at the end of caspofungin therapy. Eradication was considered to be "presumptive" if a patient had a complete response but culture results at follow-up were not available. "Persistence" referred to culture results that remained positive throughout and at the end of caspofungin therapy. A "microbiological relapse" indicated that negative culture results were obtained during therapy but that, subsequently, positive results were obtained at the end of caspofungin therapy or at the 4-week follow-up visit. When culture results were not available at the end of therapy, the response was designated "indeterminate." Persistence, relapse, and an indeterminate response were all considered unfavorable mycological outcomes. Patients classified as having complete or partial clinical response but persistent results of microbiological culture of sputum or BAL samples were classified as having microbiological failure but not clinical failure. Mycological responses were not determined for patients with positive histological, antigen, or PCR results only.

Assessment of safety and tolerability. Patients were monitored daily for clinical adverse events (AEs) during the study and at the 4-week follow-up visit. Monitoring of laboratory tests was performed at least twice weekly throughout the therapy period and at follow-up. All AEs that arose during treatment and follow-up were rated by the investigator with regard to severity and the likelihood of an association with the study drug. The tolerability of caspofungin therapy was assessed and recorded daily by the investigator and was based on inspection and the patient's comments regarding the presence or absence of signs of intolerance at the local site of infusion (i.e., erythema, thrombophlebitis, etc.). Tolerability was rated as "well," "moderately well," and "poorly" tolerated. Possible infusion-related reactions to caspofungin (e.g., rigors and anaphylaxis) were also noted and tabulated.

Statistical analysis. This study was an open, noncomparative estimation study. The primary evaluation for efficacy was the proportion of patients with a favorable (complete or partial) response by the end of intravenous therapy. For each proportion, the 95% CI was calculated as an exact confidence interval based on the binomial distribution. At least 30% of the patients were expected to have a favorable clinical response by the end of caspofungin therapy.

Two separate efficacy analyses were prespecified: a modified intention-to-treat (MITT) analysis and an evaluable-patients (EP) analysis. The MITT analysis was the primary efficacy

analysis. Inclusion in the MITT analysis required that patients had protocol-defined proven or probable IA and had received ⩾1 dose of caspofungin and that sufficient data were available for assessment. For inclusion in the EP analysis, the patient needed to fulfill the MITT requirements, as well as the following criteria: (1) patient had not received any concomitant systemic antifungal therapy while receiving caspofungin therapy; (2) patient did not have any protocol violations that would interfere with the efficacy assessment; (3) patient had an end-of-treatment clinical evaluation; and (4) patient had received at least 7 days of study therapy. Exploratory analyses of responses in subgroups of patients were performed by Fisher's exact test or χ^2 analysis, as appropriate.

RESULTS

A total of 90 patients were enrolled in the study. Five patients did not meet the diagnostic criteria at study entry (no confirmed evidence of IA) and were excluded from the efficacy analyses. Two patients who met the protocol-defined criteria for diagnosis had no data on which to base an assessment of response; data from these 2 patients also were not included in any efficacy analyses. Thus, assessments of efficacy were based on data from the remaining 83 patients. All 90 patients were considered to be assessable for the safety of therapy.

Patient Demographic and Clinical Characteristics

General characteristics. Baseline characteristics of the 83 patients are presented in table 1. The majority of patients were male, and age ranged from 15 to 73 years (median, 51 years).

Underlying medical conditions. Most patients had underlying conditions associated with immunosuppression, including hematologic malignancies, solid-organ transplantation, HSCT, and neutropenia.

Site of IA. Pulmonary aspergillosis was the most common type of infection, occurring in 64 patients (77.1%). Five of these patients also had multiple CNS lesions that were classified as evidence of possible CNS aspergillosis. Extrapulmonary aspergillosis was diagnosed in the remaining 19 patients (22.9%), including 13 with disseminated infection.

Refractory to or intolerant of therapy. Sixty-six patients (79.5%) were refractory to standard antifungal therapy, and another 5 patients (6.0%) were considered by the expert panel to be refractory to prophylaxis with standard antifungal compounds (table 2). Of the 71 patients who were refractory to therapy, 47 (66.2%) and 35 (49.3%) patients had received >14 days and >21 days of previous antifungal therapy, respectively (table 3).

Duration of Therapy

Caspofungin was administered for a median duration of 28 days (range, 1–162 days). All but 1 patient received a 70-mg

Table 1. Baseline demographic and clinical characteristics of patients with invasive aspergillosis who were included in the efficacy analyses for caspofungin therapy.

Characteristic	No. (%) of patients (n = 83)
Sex	
Male	58 (69.9)
Female	25 (30.1)
Race	
White	78 (94.0)
Hispanic	3 (3.6)
Other	2 (2.4)
Age, years[a]	
<18	1 (1.2)
18–40	27 (32.5)
41–65	42 (50.6)
>65	13 (15.7)
Site of *Aspergillus* infection[b]	
Pulmonary	
Proven	34 (41.0)
Probable	30 (36.1)
Sinus	4 (4.8)
CNS	1 (1.2)
Sinopulmonary	1 (1.2)
Disseminated	13 (15.7)
Response to standard antifungal therapy	
Refractory	66 (79.5)
Refractory to prophylaxis	5 (6.0)
Intolerant	12 (14.5)
Underlying condition	
Hematologic malignancy[c]	60 (72.3)
Acute leukemia[d]	30 (36.1)
Chronic or other type of leukemia[e]	11 (13.2)
Hodgkin lymphoma	2 (2.4)
Non-Hodgkin lymphoma	8 (9.6)
Multiple myeloma	3 (3.6)
Myelodysplastic syndrome	6 (7.2)
Solid-organ transplantation[f]	9 (10.8)
Solid tumor[g]	3 (3.6)
Other risk factors[h]	11 (13.3)
Neutrophil count at enrollment, cells/μL	
<500 (neutropenic)	19 (22.9)
⩾500 (nonneutropenic)	64 (77.1)

[a] Median age, 51.0 years (range, 15–73 years).

[b] All extrapulmonary cases of infection required proven (definite) diagnosis. Patients with allergic bronchopulmonary aspergillosis, aspergilloma, or ocular disease or with disease limited to sinusitis or external otitis (in the absence of tissue invasion) were not eligible for enrollment.

[c] Twenty-five patients had undergone bone-marrow or peripheral stem-cell transplantation, including 21 patients who had undergone allogeneic transplantation.

[d] Includes 23 patients with acute myelogenous leukemia, 6 patients with acute lymphoblastic leukemia, and 1 patient with acute undifferentiated leukemia.

[e] Includes 6 patients with chronic myelogenous leukemia, 2 with chronic lymphocytic leukemia, 2 with hairy-cell leukemia, and 1 with large granular lymphocytic leukemia.

[f] Includes 5 lung, 2 heart, 1 liver, and 1 kidney transplantation.

[g] All were cases of lung cancer (1 adenocarcinoma and 2 cases of non–small cell cancer).

[h] Includes corticosteroid use by 4 patients and skull trauma, methotrexate, prior mycobacterial infection of the lung, and chronic graft-versus-host disease in 1 patient each; 3 patients did not have any discernible risk factors.

Table 2. Distribution of patients with invasive aspergillosis, by response to standard antifungal therapy and site of infection.

Response to standard antifungal therapy	No. (%) of patients, by site of infection		
	Pulmonary (n = 64)	Extrapulmonary (n = 19)	Total (n = 83)
Refractory[a]			
To therapy	48 (75.0)	18 (94.7)	66 (79.5)
To prophylaxis	5 (7.8)	0	5 (6.0)
Total	53 (82.8)	18 (94.7)	71 (85.5)
Intolerant	11 (17.2)	1 (5.3)	12 (14.5)

[a] Includes patients who were both refractory to and intolerant of standard antifungal therapy.

loading dose on the first day of therapy, and all but 3 patients received a 50-mg maintenance dose of caspofungin daily.

Efficacy (Clinical Response)

Of the 83 assessable patients included in the MITT analysis (primary analysis), 37 patients (44.6%) had a favorable response by the end of intravenous therapy (table 4). In the MITT analysis, 6 patients (7%) were classified as having stable disease and 40 (48%) as having therapy failure. In the EP analysis (secondary analysis), 37 (56.1%) of 66 patients showed a favorable response (table 4).

Factors Influencing Efficacy Outcome

The proportions of patients with a favorable response are summarized in table 5 by site of infection. Significantly more favorable responses were observed among patients with hematological malignancies, compared with those who had undergone allogeneic HSCT ($P < .01$), and among patients enrolled because of intolerance to therapy, compared with those enrolled because of infection refractory to therapy ($P = .03$). Trends toward a higher proportion of favorable responses were observed among patients with pulmonary disease, compared with those with extrapulmonary disease ($P = .11$), and among patients with neutropenia, compared with those without neutropenia, at baseline ($P = .11$).

Microbiological Response

Aspergillus species were isolated from 65 patients (78.3%) at baseline. The diagnosis of IA in the remaining 18 patients was based on results of antigen detection and/or histopathological studies. By the end of caspofungin therapy, 22 (33.8%) of the 65 patients had a favorable microbiological response (eradication or presumptive eradication). Twenty of these 22 patients had a favorable clinical response. Eradication of the infecting pathogen was achieved for 13 (28%) of 47 patients with *Aspergillus fumigatus* infection, 7 (54%) of 13 with *Aspergillus flavus* infection, 1 (25%) of 4 with *Aspergillus niger* infection, and 0 of 1 with *Aspergillus terreus* infection.

Relapse

Of the 37 patients who had a favorable response by the end of therapy, 31 were evaluated at the 4-week follow-up visit. Most (90.6%) had received suppressive itraconazole therapy during the follow-up period. Three (9.7%) of these 31 patients had a relapse of IA, but only 1 case of relapse was confirmed microbiologically. All 3 cases of relapse occurred in patients receiving suppressive itraconazole.

Mortality

Of the 83 assessable patients, 40 (48.1%) died during the study (during treatment or follow-up), including 14 during the 4-week follow-up period and 6 thereafter. Ten (12.1%) and 13 (15.7%) of the 83 patients were considered by the investigator to have died directly as a result of aspergillosis or of other infection-related (respiratory) complications, respectively. Causes of death for the other 17 patients included progression of malignancy, leukemic relapse, and bacterial sepsis.

Drug Safety and Tolerability

Of the 90 patients enrolled in the study who received at least 1 dose of study drug, 84 (93.3%) developed at least 1 clinical AE. However, only 11 patients (12.2%) had a clinical AE that was related (either possibly, probably, or definitely) to caspofungin therapy. The most common drug-related AEs (i.e., incidence >2%) are listed in table 6. Only 1 patient (1.2%) was considered by the investigator to have had a serious drug-related clinical AE (table 6). Fifty-three (58.9%) of the 90 pa-

Table 3. Distribution of patients with invasive aspergillosis, by type and duration of previous antifungal therapy.

Previous antifungal therapy	No. (%) of patients, by response to therapy	
	Refractory[a] (n = 71)	Intolerant (n = 12)
Type		
Amphotericin B deoxycholate	14 (19.7)	6 (50.0)
Lipid formulation of amphotericin B (any preparation)	20 (28.2)	3 (25.0)
Itraconazole	14 (19.7)	1 (8.3)
Voriconazole	1 (1.4)	0
>1 Antifungal drug	22 (31.0)	2 (16.7)
Duration, days		
⩽14	24 (33.8)	10 (83.3)
15–21	12 (16.9)	0
22–28	3 (4.2)	0
>28	32 (45.1)	2 (16.7)

[a] Includes patients who were both refractory to and intolerant of previous antifungal therapy.

Table 4. Efficacy outcome at the end of caspofungin therapy.

Analysis, type of response to caspofungin therapy	No. (%) of patients	95% CI
Primary[a]		
Complete	4 (5)	…
Partial	33 (40)	…
Total	37 (44.6)	33.7–55.9
Secondary[b]		
Complete	4 (6)	…
Partial	33 (50)	…
Total	37 (56.1)	43.3–68.3

[a] For modified intent-to-treat population, percentages are based on a total of 83 assessable patients, which included patients receiving at least 1 dose of study drug and having sufficient information to permit evaluation. Of the 83 assessable patients, 6 (7%) were classified as having stable disease and 40 (48%) as having therapeutic failure.

[b] For evaluable patients, percentages are based on a total of 66 assessable patients, which included patients who had received at least 7 days of caspofungin therapy.

tients developed at least 1 laboratory AE, but only 12 patients (13.3%) were considered by the investigator to have had a drug-related AE.

In general, infusion of caspofungin was well tolerated: 88 patients (97.8%) received a tolerability rating of "well tolerated" at the local site of infusion, and 2 patients received a rating of "moderately well tolerated." Eighty (88.9%) of the 90 patients received an overall rating of "no systemic infusion-related events." The remaining 10 received an overall rating of "mild systemic infusion-related events" at the end of caspofungin therapy. The most common infusion-related events (all occurring in ⩽5 patients) were fever, nausea, and vomiting.

DISCUSSION

To our knowledge, this clinical trial is the first study to document the efficacy and study of an echinocandin for the treatment of IA. Caspofungin was effective in the treatment of IA in patients refractory to standard therapy. The results of this pivotal study led to the first approval in North America and the European Union of the use of an echinocandin for the treatment of IA in patients intolerant of or refractory to conventional antifungal therapy.

In an attempt to establish a clear understanding of the response to antifungal therapy, this study used stringent criteria for inclusion and adhered to rigid definitions for favorable outcomes. Diagnoses of IA were based on a set of definitions that were similar to the European Organization for Research and Treatment of Cancer–Mycoses Study Group criteria for proven and probable IA [32]. Furthermore, efficacy was assessed by use of a conservative MITT analysis.

Another salient feature of this study was that most patients were enrolled because of refractory aspergillosis. This study included a relatively high proportion (85.5% patients) of cases of refractory infection. In this population, infection had been heavily pretreated. Approximately two-thirds of the patients had received >14 days of standard therapy before enrollment, and one-third of these patients were refractory to >1 antifungal

Table 5. Distribution of patients with a favorable response to caspofungin therapy, by factors influencing efficacy outcome.

Factor	No. of patients with favorable response/ total no. of assessable patients (%)[a]
Site of IA[b]	
Pulmonary	
Proven	13/34 (38.2)
Probable	19/30 (63.3)
Total	32/64 (50.0)
Extrapulmonary	
Disseminated	3/13 (23.1)
Sinus	1/4 (25.0)
Sinopulmonary	0/1
CNS[c]	1/1 (100.0)
Total	5/19 (26.3)
Underlying condition	
Hematological malignancy[d,e]	25/60 (41.7)
Allogeneic HSCT[e]	3/21 (14.3)
Solid-organ transplantation[f]	4/9 (44.4)
Solid tumor	3/3 (100.0)
Other	5/11 (45.5)
Response to standard antifungal therapy[g]	
Refractory	28/71 (39.4)
Intolerant	9/12 (75.0)
Neutrophil count at baseline, cells/μL[h]	
ANC <500 (neutropenic)	5/19 (26.3)
ANC ⩾500 (nonneutropenic)	32/64 (50.0)
Corticosteroid therapy (prednisone or equivalent) at baseline, mg/day[i]	
>20	10/28 (35.7)
⩽20	27/55 (49.1)

NOTE. ANC, absolute neutrophil count; HSCT, hematopoietic stem-cell transplantation; IA, invasive aspergillosis.

[a] Favorable response included both complete and partial response to caspofungin therapy.

[b] $P = .11$, for pulmonary vs. extrapulmonary subgroups.

[c] Includes all patients with any evidence of proven CNS disease. Among all patients with proven or possible CNS aspergillosis, including those with disseminated infection, 2 (33%) of 6 patients had a favorable response.

[d] Includes a favorable response in 16 (53.3%) of 30 patients with acute leukemia, 1 (9.1%) of 11 patients with chronic or other leukemia, 4 (40%) of 10 patients with lymphoma, 2 (33.3%) of 6 patients with myelodysplastic syndrome, and 2 (66.7%) of 3 patients with multiple myeloma.

[e] $P < .01$, for hematological malignancy vs. allogeneic HSCT.

[f] Includes a favorable response in 1 (20%) of 5 patients with lung transplant, 2 (100%) of 2 patients with heart transplant, 1 (100%) of 1 patient with kidney transplant, and 0 of 1 patient with liver transplant.

[g] $P = .03$, for refractory vs. intolerant.

[h] $P = .11$, for neutropenic vs. nonneutropenic at baseline.

[i] $P = .35$, for >20 mg/day vs. <20 mg/day.

drug. Given this challenging patient population, the achievement of a favorable response in 39% of patients refractory to standard therapy is particularly noteworthy. This rate of response, combined with a rate of favorable response of 75% among patients intolerant to therapy, yielded an overall rate of favorable response of 45%. However, because only 1 patient had previously received voriconazole, these results do not necessarily predict a salvage response for those patients refractory to voriconazole therapy.

Patients with pulmonary aspergillosis tended to respond better than those with extrapulmonary aspergillosis (favorable response in 50.0% vs. 26.3% of patients, respectively). Nevertheless, favorable responses were achieved with caspofungin therapy in patients with disseminated disease, CNS involvement, and sinusitis. This lower rate of response among patients with extrapulmonary aspergillosis, which usually is a disseminated infection, is consistent with results of previous studies of IA [13, 18].

Reversal of immunosuppression is a critical factor in the prognosis for patients with IA [33, 34]. The rate of favorable response (14.3%) to caspofungin observed among patients who had received an allogeneic HSCT was lower than the overall rate of favorable response (44.6%); this finding is typical for this risk factor and is related to the need for ongoing immunosuppressive therapy for the prevention or treatment of graft-versus-host disease [4]. Patients with neutropenia at baseline also tended to have a lower overall rate of favorable response, compared with that among patients without neutropenia. However, 4 of 5 patients with neutropenia who had a favorable response had clinical improvement prior to neutrophil recovery, including 1 patient who had neutropenia for >3 weeks while receiving the study drug.

The finding that most patients with a favorable response had a partial response, rather than a complete response, reflects the stringent requirement that a complete response required resolution of all attributable signs, symptoms, and radiographic findings. Even the presence of a small residual pulmonary infiltrate would have resulted in the patient being classified as having a partial response. Clinical response rates in this study compared favorably to those of patients in a carefully selected historical control study [35], as well as to results of recent studies of salvage therapy with voriconazole [18, 19, 36].

Caspofungin therapy was well tolerated by most patients, and drug-related toxicity was minimal. The low frequency and the pattern of drug-related clinical and laboratory AEs in this study were similar to those found in comparative therapeutic trials of esophageal candidiasis and candidemia [30, 31, 37], despite the long-term duration of therapy (mean, 34.7 days) and the inclusion of a highly immunocompromised population.

In conclusion, on the basis of analyses of well-documented cases of IA in patients predominantly refractory to standard therapy, caspofungin was found to be an effective and very well-tolerated alternative for salvage treatment of IA. Randomized controlled trials should be undertaken to further determine the usefulness of caspofungin for primary treatment of IA. In addition, given its novel mode of action, relative to the triazole and polyene agents, the availability of this agent should offer possibilities for combination therapy for the treatment of these potentially life-threatening infections [38–41].

Table 6. Drug-related adverse events in patients with invasive aspergillosis, during caspofungin therapy.

Type of adverse event	No. (%) of patients (n = 90)
Clinical[a]	11 (12.2)
Asthenia/fatigue	2 (2.2)
Fever	2 (2.2)
Infusion-vein complication	2 (2.2)
Flushing	2 (2.2)
Nausea	2 (2.2)
Vomiting	2 (2.2)
Diarrhea	1 (1.1)
Rash	1 (1.1)
Laboratory[b]	12 (13.6)
Elevated serum ALT level	1 (1.1)
Elevated serum AST level	1 (1.1)
Elevated serum alkaline phosphatase level	2 (2.3)
Elevated total serum bilirubin level	1 (1.1)
Elevated BUN level	1 (1.1)
Elevated serum creatinine level	1 (1.1)
Low serum potassium level	2 (2.3)
Elevated serum calcium level	1 (1.1)
Elevated eosinophil count	2 (2.3)
Elevated urine protein level	3 (3.4)

NOTE. Adverse events were determined by the investigator to be possibly, probably, or definitely drug related. Although patients may have experienced a drug-related adverse event ⩾2 times, patients were counted only once within a category, and the same patient may have been counted in different categories. ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; HSCT, hematopoietic stem-cell transplantation.

[a] Of the 66 patients reported to have had a serious clinical adverse event, only 1 patient (1.2%) was considered by the investigator to have had a drug-related adverse event. The patient was a 38-year-old man who developed refractory proven pulmonary aspergillosis after allogeneic HSCT for treatment of multiple myeloma. While receiving caspofungin, he developed progressive pulmonary infiltrates. Caspofungin was discontinued, and therapy with methylprednisolone, ganciclovir, trimethoprim-sulfamethoxazole, and amphotericin B lipid complex was started. The patient underwent bronchoscopy with biopsy, but no specific etiology was identified. Therefore, the investigator reported the development of pulmonary infiltrates as possibly related to caspofungin therapy.

[b] Percentage for total laboratory adverse events is based on the no. of patients with laboratory adverse events/88 patients with data from laboratory testing. Among the 3 (3.4%) patients reported to have had a serious laboratory adverse event, only 1 patient (1.1%) was considered to have had a drug-related adverse event. The patient was a 23-year-old man who had undergone allogeneic HSCT for treatment of Hodgkin disease and who developed disseminated aspergillosis refractory to liposomal amphotericin B. Hypercalcemia (12.8 mg/dL) developed on day 32 of caspofungin therapy and was treated with pamidronate. The investigator attributed the hypercalcemia as probably being related to caspofungin.

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