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A Prospective, Multicenter Study of Caspofungin for the Treatment of Documented *Candida* or *Aspergillus* Infections in Pediatric Patients

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00082524).

What's Known on This Subject

Caspofungin is approved for the treatment of invasive fungal infections in adults but has not been studied extensively in children.

What This Study Adds

To our knowledge, this is the first prospective clinical study of caspofungin for the treatment of documented invasive fungal infections in children.

ABSTRACT

OBJECTIVE. We evaluated the safety, tolerability, and efficacy of caspofungin in pediatric patients with invasive aspergillosis, invasive candidiasis, or esophageal candidiasis.

METHODS. This was a multicenter, prospective, open-label study in children 3 months to 17 years of age with proven or probable invasive aspergillosis, proven invasive candidiasis, or proven esophageal candidiasis. All of the patients received caspofungin 70 mg/m² on day 1, followed by 50 mg/m² per day (maximum: 70 mg/day), as primary or salvage monotherapy. Favorable response was defined as complete resolution of clinical findings and microbiologic (or radiographic/endoscopic) eradication (complete response) or significant improvement in these parameters (partial response). Efficacy was assessed at the end of caspofungin therapy in patients with a confirmed diagnosis who received ≥1 dose of caspofungin. The primary safety evaluation was the proportion of patients with clinical or laboratory drug-related adverse events.

RESULTS. Of the 49 patients enrolled, 3 were <2 years of age, 30 were 2 to 11 years of age, and 16 were 12 to 17 years of age. Forty-eight patients had confirmed disease: invasive aspergillosis (10), invasive candidiasis (37), and esophageal candidiasis (1). Eight of 10 patients with invasive aspergillosis had pulmonary involvement; 34 of 37 patients with invasive candidiasis had candidemia. Caspofungin was given for 2 to 87 days. Success at end of therapy was achieved in 5 of 10 patients with invasive aspergillosis, 30 of 37 with invasive candidiasis, and 1 of 1 with esophageal candidiasis. One patient (invasive candidiasis) relapsed during the 28-day follow-up period. Drug-related clinical or laboratory adverse events occurred in 27% and 35% of patients, respectively. There were no serious drug-related adverse events or discontinuations of caspofungin because of toxicity.

CONCLUSIONS. Caspofungin was generally well tolerated in pediatric patients aged 6 months through 17 years. Efficacy outcomes in patients with invasive aspergillosis or invasive candidiasis were consistent with previous adult studies in these indications. *Pediatrics* 2009;123:877–884

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Key Words
caspofungin, echinocandin, invasive aspergillosis, invasive candidiasis, pediatric patients

Abbreviations
ULN— upper limit of normal
AST—aspartate aminotransferase
ALT—alanine aminotransferase
CI— confidence interval
CNS— central nervous system
MIC—minimum inhibitory concentration
ABLC—amphotericin B lipid complex

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THE FREQUENCY AND severity of invasive fungal infections in both adults and children has increased steadily over the past 2 decades.[1–5] The increase in invasive fungal infections is likely attributable to an increased prevalence of susceptible hosts who receive intensive care therapies, cytotoxic agents, immunosuppressive therapies associated with transplantation, and broad-spectrum antibiotics.[6–8] *Candida* spp. and *Aspergillus* spp. are the most common invasive fungal infections in children and are associated with significant morbidity and mortality. The mortality rates in children with candidemia range from 16% to 31%,[9–11] whereas invasive aspergillosis in children is associated with even greater mortality, approaching rates as high as 77%.[12–15]

In response to the increased incidence and high mortality rates associated with invasive fungal infections, novel antifungal agents have been developed to expand the breadth and effectiveness of treatment options available to clinicians. Caspofungin is an echinocandin antifungal agent with activity against *Candida* and *Aspergillus* spp.[16] that has been shown effective as a salvage therapy for invasive aspergillosis[17] and as primary treatment of esophageal candidiasis,[18] candidemia,[19] and other invasive *Candida* infections[20] in adults. Caspofungin is associated with fewer drug-related adverse events, fewer infusion-related events, and less nephrotoxicity than conventional[18,19] or liposomal amphotericin B.[21] The favorable efficacy and safety profile documented in adults make caspofungin an attractive choice also for pediatric patients. The purpose of this study was to evaluate the safety and efficacy of caspofungin in the treatment of documented invasive *Aspergillus* or *Candida* infection in the pediatric population.

METHODS

Patients

Children and adolescents 3 months to 17 years of age were eligible if they met criteria for documented invasive aspergillosis, invasive candidiasis, or esophageal candidiasis according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group.[22] Diagnosis of infection was based on clinical history, signs and symptoms of illness, radiographic evidence, and positive histopathology and/or culture for fungal organisms. Diagnosis of invasive candidiasis required ≥1 positive culture of a *Candida* species from blood or another normally sterile body site obtained by sterile procedure within 4 days of study entry. Patients with proven or probable invasive aspergillosis were enrolled only if they had failed to respond to or were intolerant of standard antifungal therapy (eg, conventional or lipid formulations of amphotericin B, itraconazole, and voriconazole). Because of the difficulties inherent in the microbiologic diagnosis of *Aspergillus* infection, histopathology/cytopathology and galactomannan enzyme-linked immunosorbent assay, along with appropriate radiographic and clinical findings, were also acceptable methods of diagnosis. Exclusion criteria for all of the patients included acute or chronic hepatic disease; concomitant rifampin, cyclosporin A, or systemic antifungal therapy; bilirubin >3 times the upper limit of normal (ULN) for age; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the ULN for age; or platelet count <5000/μL.

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations. The protocol was reviewed by each center's ethics review committee/institutional review board. Written informed consent was obtained from the legal guardian of each patient before study procedures were performed.

Study Design

This was an open-label, noncomparative study conducted from May 2004 through July 2007 to evaluate the safety, tolerability, and efficacy of caspofungin in ~50 children or adolescents with documented *Candida* or *Aspergillus* infection. Twelve centers in the United States, European Union, Israel, and Taiwan enrolled patients. All of the patients received caspofungin monotherapy 50 mg/m^2 per day (based on body surface area; maximum: 70 mg/day) after a 70-mg/m^2 loading dose on day 1. This dosage was based on pharmacokinetic studies in children 2 to 17 years of age[23] and 3 to 24 months of age.[24] Caspofungin was given by intravenous infusion over 1 hour. The duration of therapy was individualized for each patient according to existing treatment guidelines of the Infectious Diseases Society of America.[25,26] Patients who failed to improve clinically after ≥4 days of caspofungin therapy could receive 70 mg/m^2 (maximum: 70 mg/day) until therapy was discontinued; if drug-related toxicity developed, the caspofungin dose could revert to 50 mg/m^2.

Assessments

Efficacy

Assessment of signs and symptoms of the underlying fungal infection were performed at screening, daily during caspofungin therapy, and at the 14-day and 28-day follow-up visits. In patients with candidemia, blood cultures were drawn daily until they were negative for ≥48 hours. Investigators monitored the resolution or progression of each patient's fungal infection by assessment of signs and symptoms, cultures, and/or radiographic studies, as appropriate.

The primary efficacy end point was the proportion of patients with a favorable response (either complete or partial) at the end of caspofungin therapy (Table 1). Patients with a favorable response at the end of caspofungin therapy were assessed for relapse 14 and 28 days later. Criteria for favorable response differed among the 3 infection types (see Table 1). For invasive aspergillosis, efficacy was based on clinical evaluation that incorporated signs/symptoms of *Aspergillus* infection, radiographic data, and other relevant information (eg, histopathology and/or culture data). For invasive candidiasis, efficacy was based on the overall response: a favorable overall response required both a favorable clinical response and a favorable microbiologic response. For

TABLE 1 Response Definitions

Response Type	Invasive Aspergillosis	Invasive Candidiasis	Esophageal Candidiasis
Favorable response	Complete or partial clinical response	Complete or partial clinical response plus microbiological eradication or presumed eradication[a,b]	Complete or partial clinical response, which included both symptomatic and endoscopic criteria
Complete clinical response	Resolution of symptoms and of all radiographic and other relevant abnormalities attributed to *Aspergillus* infection	Resolution of all signs and symptoms and of all relevant radiographic findings	Resolution of all signs and symptoms and no remaining lesions seen on endoscopy or a reduction of lesions by ≥2 stepwise grades
Partial clinical response	Clinically significant improvement in symptoms and radiographic and other relevant investigative abnormalities attributed to *Aspergillus* infection	Improvement of most signs and symptoms and improvement in relevant radiographic findings	Improvement of signs and symptoms and reduction of endoscopic lesions by 1 stepwise grade or no endoscopy performed at end of caspofungin therapy

[a] For patients with candidemia, demonstration of negative blood cultures for ≥48 hours was required.
[b] Presumed eradication was only applicable to nonblood cases of invasive candidiasis.

esophageal candidiasis, efficacy was based on assessments of signs and symptoms and endoscopic findings.

Safety and Tolerability

An overall clinical assessment, including physical examination, vital signs, and laboratory tests, was performed at least twice weekly during caspofungin therapy, on the last day of caspofungin therapy, and at the 14-day post-therapy visit. Patients were monitored daily for adverse events during caspofungin therapy and for 14 days after discontinuation. The primary safety end point was the proportion of patients with drug-related clinical or laboratory adverse events. Patients were also monitored for local infusion-related tolerability and systemic infusion-related events that occurred during or within 1 hour after the caspofungin infusion.

Statistical Analyses

Formal hypothesis testing was not performed in this study. Confidence intervals (CIs) were calculated for estimation purposes only and represent the range of truly existing proportions that might be observed in a larger similar population. Patients with a confirmed diagnosis who received ≥1 dose of caspofungin were included in the efficacy analysis. Safety evaluations included all of the patients who received ≥1 dose of caspofungin. The proportion of patients and its respective 95% Clopper-Pearson exact CI were calculated for the primary end points.

RESULTS

Forty-nine patients were enrolled in the study: 10 with invasive aspergillosis, 38 with invasive candidiasis, and 1 with esophageal candidiasis.

Patient Characteristics

Baseline characteristics of the patients with invasive aspergillosis are shown in Table 2. The mean age was 8.3 years (range: 3.0–16.0 years); 80% were under 12 years of age. All 10 of the patients were refractory to previous antifungal treatment: 6 had received amphotericin B (3 for 7–14 days; 3 for 15–28 days), 1 had received itraconazole (for 31 days), 1 had received voriconazole (for 7 days), and 2 had received amphotericin plus voriconazole (for 25 and 33 days, respectively). Eight patients had pulmonary involvement, 6 with pulmonary aspergillosis and 2 with multiple sites of infection (Table 2). Hematologic malignancy was a predisposing condition in 6 patients (60%), 2 of whom had received an allograft of hematopoietic progenitors, and 30% of patients were neutropenic (defined as neutrophil count $<500/\mu L$) at study entry. The mean duration of caspofungin therapy was 42.7 days (range: 6.0–87.0 days) in patients with invasive aspergillosis.

In the patients enrolled with invasive candidiasis, candidemia accounted for the majority of cases (92%), and most patients (82%) received caspofungin as the primary treatment (Table 2). The mean age was 7.9 years (range: 0.5–17.0 years), with 66% <12 years of age. Common risk factors included the presence of an intravascular catheter (79%), the use of broad-spectrum antibiotics (74%), total parenteral nutrition (63%), and immune suppression because of underlying disease or its treatment (55%). The majority of these patients (84%) were not neutropenic at study entry. The most common primary background conditions were underlying malignancies (34%), congenital disorders (21%), and solid organ transplant (13%). The most common malignancies were medulloblastoma (8%), neuroblastoma (5%), and acute lymphoblastic leukemia (5%). Cystic fibrosis (5%) was the most common congenital disorder, and liver transplantation (8%) was the most common solid organ transplantation. The mean duration of caspofungin therapy was 11.8 days (range: 2.0–42.0 days) in patients with invasive candidiasis.

One patient with esophageal candidiasis (because of *C albicans*) was enrolled and received caspofungin as primary treatment for 32 days. This patient was a 17-year-old boy with recurrent acute myeloid leukemia and a history of allogeneic bone marrow transplantation.

TABLE 2 Baseline Characteristics in Patients With Invasive *Aspergillosis* and Invasive *Candidiasis*

Characteristic	*N* (%)
Patients with aspergillosis, *n*	10
Gender	
Male	8 (80.0)
Female	2 (20.0)
Race	
White	6 (60.0)
Asian	4 (40.0)
Age, y	
2–6	3 (30.0)
7–11	5 (50.0)
12–14	1 (10.0)
15–17	1 (10.0)
Site of infection	
Definite pulmonary	2 (20.0)
Probable pulmonary[a]	4 (40.0)
Definite middle ear, right	1 (10.0)
Definite intracranial	1 (10.0)
Multiple sites[b]	2 (20.0)
Reason for study entry	
Refractory	8 (80.0)
Both refractory and intolerant	2 (20.0)
Predisposing conditions	
Hematologic malignancy	6 (60.0)
Allogeneic bone marrow transplant	1 (10.0)
Allogeneic peripheral stem cell transplant	1 (10.0)
Solid tumor	2 (20.0)
Corticosteroid therapy[c]	1 (10.0)
Chronic granulomatous disease	1 (10.0)
Neutropenia status at study entry[d]	
Nonneutropenic	7 (70.0)
Neutropenic	3 (30.0)
Patients with candidiasis, *n*	38
Gender	
Male	22 (57.9)
Female	16 (42.1)
Race	
White	23 (60.5)
Black, of African heritage	6 (15.8)
Asian	5 (13.2)
American Indian or Alaska Native	2 (5.3)
Multiracial	2 (5.3)
Age	
3–23 mo	3 (7.9)
2–6 y	16 (42.1)
7–11 y	6 (15.8)
12–14 y	7 (18.4)
15–17 y	6 (15.8)
Site of infection	
Blood	35 (92.1)
Psoas muscle abscess	1 (2.6)
Multiple sites[e]	2 (5.3)
Reason for study entry	
Primary therapy	31 (81.6)
Salvage therapy (refractory)	7 (18.4)
Risk factors[f]	
Active malignancy	12 (31.6)
Broad spectrum antibiotics	28 (73.7)
Diabetes mellitus	1 (2.6)
Immunosuppression	21 (55.3)
Major surgery	8 (21.1)
Neutropenia	7 (18.4)
Total parenteral nutrition	24 (63.2)
Transplant[g]	9 (23.7)
Vascular catheter	30 (78.9)
Other[h]	2 (5.3)
Neutropenia status at study entry	
Nonneutropenic	32 (84.2)
Neutropenic	6 (15.8)

[a] Data are according to criteria developed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group.[22]
[b] Data include 1 patient with probable pulmonary and definite skin aspergillosis and 1 patient with probable pulmonary, CNS, and definite skin aspergillosis.
[c] Data include methylprednisolone for severe aplastic anemia.
[d] Data are defined as neutrophil count $<500/\mu L$.
[e] Data include 1 patient with blood and peritoneal fluid candidiasis and 1 with nasal cavity and hepatosplenic candidiasis.
[f] Patients may appear in >1 risk category.
[g] Data include solid organ ($n = 5$) and bone marrow ($n = 4$) transplant.
[h] Data include 1 patient listed for a heart transplant and 1 on chemotherapy.

Efficacy

Five (50%) of the 10 patients with invasive aspergillosis had a favorable clinical response at the end of caspofungin therapy (Table 3). Three of these patients received chemotherapy during caspofungin treatment, and a fourth patient received methylprednisolone for graft-versus-host disease prophylaxis. All 5 of the patients continued to have a favorable clinical response at both the 14- and 28-day posttherapy follow-up visits. Of the 5 patients who had an unfavorable clinical response, 1 died on day 29 of caspofungin therapy (because of worsening acute myeloid leukemia, sepsis, and pneumonia), and 4 received other antifungal therapy after caspofungin was stopped (on days 6, 8, 10, and 85, respectively); these 4 patients also died, despite treatment (ranging from 2 to 33 days) with voriconazole in 1 patient, AmBisome in 1, and AmBisome plus voriconazole in 2. All 5 of the patients who had an unfavorable response were either neutropenic at study entry and/or received chemotherapy during the study because of worsening of their underlying condition.

The response rate was consistent across age groups: favorable responses were seen in 4 of 8 children (range: 2–11 years old) and in 1 of 2 adolescents (range: 12–17 years old). Two of 6 patients with hematologic malignancy and 3 of 4 patients with solid tumor or other underlying conditions had a favorable response at the end of caspofungin therapy. Response rates were lowest in patients with multiple sites of infection (0 of 2 vs 3 of 6 with pulmonary infection and 2 of 2 with central nervous system [CNS] or middle ear infection) or neutropenia at study entry (0 of 3 vs 5 of 7 who were nonneutropenic). Four patients had baseline *Aspergillus* isolates; 2 of these patients had a favorable response (1 with *A fumigatus* [CNS] and 1 with *A terreus* [middle ear]). The other *Aspergillus* isolates were *A flavus* (pulmonary and skin) and *A niger* (pulmonary). All 4 of the isolates had low minimum inhibitory concentrations (MICs) to caspofungin (between 0.03 and 0.06 μg/mL).

One patient was excluded from the efficacy analysis

TABLE 3 Efficacy and Safety Outcomes

Variable	Invasive Aspergillosis (*N* = 10)	Invasive Candidiasis (*N* = 38)	Total (*N* = 49)[a]
Response rates and relapse rates by infection type[b]			
Favorable outcome at end of therapy, *n* (%) [95% CI]	5 (50.0) [18.7–81.3]	30 (81.1) [64.8–92.0]	36 (75.0)[a]
Complete response, *n* (%) [95% CI]	3 (30.0) [6.7–65.2]	30 (81.1) [64.8–92.0]	34 (70.8)[a]
Partial response, *n* (%) [95% CI]	2 (20.0) [2.5–55.6]	0 (0.0) [0–0]	2 (4.2)
Relapse at 14 d, *n*/*N* (%)	0/5 (0.0)	0/28 (0.0)	0/34 (0.0)
Relapse at 28 d, *n*/*N* (%)	0/5 (0.0)	1/28 (3.6)	1/34 (2.9)
No. (%) of patients with clinical or laboratory adverse events			
Drug-related adverse events[c]			
Clinical, *n* (%) [95% CI]	4 (40.0) [12.2–73.8]	9 (23.7) [11.4–40.2]	13 (26.5) [15.0–41.1]
Laboratory, *n* (%)[95% CI]	2 (20.0) [2.5–55.6]	15 (39.5) [24.0–56.6]	17 (34.7) [21.7–49.6]
Most common drug-related adverse events[d]			
Fever, *n* (%)	2 (20.0)	1 (2.6)	3 (6.1)
Rash, *n* (%)	0 (0.0)	2 (5.3)	2 (4.1)
ALT increased, *n*/*N*(%)	2/10[e] (20.0)	5/37 (13.5)	7/48 (14.6)
AST increased, *n*/*N* (%)	2/10 (20.0)	7/37 (18.9)	9/48 (18.8)
Blood phosphorus decreased, *n*/*N*(%)[f]	0/9 (0.0)	2/37 (5.4)	2/47 (4.3)
Blood potassium decreased, *n*/*N* (%)[f]	0/10 (0.0)	3/37 (8.1)	3/48 (6.3)
Eosinophil count increased, *n*/*N* (%)[f]	0/10 (0.0)	2/36 (5.6)	2/47 (4.3)
Serious adverse events, *n* (%)[g]			
Clinical	5 (50.0)	3 (7.9)	8 (16.3)
Causing discontinuation	2 (20.0)	0 (0.0)	2 (4.1)
Deaths	5 (50.0)	0 (0.0)	5 (10.2)
Laboratory	0 (0.0)	0 (0.0)	1 (2.0)[a]

[a] Data include 1 patient with esophageal candidiasis; this patient had a complete response and a serious laboratory adverse event.
[b] One patient with invasive candidiasis was excluded from the efficacy analysis because of infection with *Trichosporon* rather than *Candida*.
[c] Data were events determined by the investigator to be possibly, probably, or definitely drug related.
[d] Data were events occurring in ≥2 patients for protocol-required laboratory tests.
[e] Data show the number of patients with the laboratory adverse event/number of patients with ≥1 measurement postbaseline for the specified test.
[f] Decreases in potassium and phosphorus were <2 times baseline or lower limit of normal; all were resolved with the continuation of therapy or during the 14-day follow-up period; increases in eosinophil count were ≤2 times ULN; 1 resolved by the 14-day follow-up visit.
[g] None of the serious adverse events were considered related to caspofungin therapy by the investigator.

of invasive candidiasis because of infection with *Trichosporon* rather than *Candida*. Thirty (81%) of the remaining 37 patients had a favorable overall response at the end of caspofungin therapy (Table 3). Of these 30 patients, 28 continued into the follow-up period and 2 discontinued from the study at the end of caspofungin therapy (1 was discharged from hospital; 1 moved to another hospital for lung transplantation). One patient had a relapse of candidiasis at the 28-day posttherapy visit (blood culture grew *C albicans*, *Proteus mirabilis*, and *Staphylococcus aureus* on day 27 of follow-up; symptoms of infection included chills and fever).

Efficacy outcomes in patients with invasive candidiasis by age and baseline factors are shown in Table 4. Favorable response rates were generally similar in patients receiving primary therapy (83%) and those receiving salvage therapy (71%). Favorable overall responses were noted across all of the *Candida* species isolated, with the exception of *C krusei*, which was isolated in only 1 patient. Notably, 7 of the 8 patients with *C parapsilosis* responded favorably at the end of caspofungin therapy. Thirty-five patients with invasive candidiasis had unique baseline fungal isolate identification and MIC testing performed by the central laboratory. MICs to caspofungin were generally low; the majority ranged from ≤0.015 to 0.500. One patient with *C lusitaniae* infection had an MIC of 1.000 and a favorable overall response to caspofungin. The overall response rates did not seem to be related to the *Candida* species or the baseline MIC for caspofungin.

Of the 7 patients with invasive candidiasis who had an unfavorable overall response at the end of caspofungin therapy, 6 had candidemia and 1 had hepatosplenic candidiasis. Three of these patients had *C tropicalis* infection: 2 had a favorable microbiologic response but were discontinued from caspofungin therapy because of suspected fungal infection of the lungs and CNS, respectively. The third patient with *C tropicalis* was a 16-year-old with relapse of acute lymphoblastic leukemia and hepatosplenic candidiasis who received caspofungin for 24 days with no improvement in radiographic findings. Two of the remaining patients with candidemia (1 *C albicans* and 1 *C krusei*) who failed caspofungin therapy were treated for only 3 and 4 days, respectively, before caspofungin was stopped to initiate combination antifungal therapy outside of the protocol.

The patient with esophageal candidiasis caused by *C albicans* had complete resolution of esophageal and oropharyngeal lesions at the end of caspofungin therapy. All of the symptoms of infection had also resolved by day 32. This patient continued to have a favorable response at the 14- and 28-day posttherapy visits.

TABLE 4 Response Rates According to Baseline Factors in Patients With Invasive Candidiasis

Baseline Factor	Favorable Response, *n/N* (%)[a]
Age	
3–23 mo	3/3 (100)
2–11 y	18/21 (85.7)
12–17 y	9/13 (69.2)
Site of infection	
Psoas muscle abscess	1/1 (100)
Multiple sites	1/2 (50.0)
Blood	28/34 (82.4)
Type of therapy	
Primary therapy	25/30 (83.3)
Salvage therapy (refractory)	5/7 (71.4)
Neutropenia status at entry	
Neutropenic	2/5 (40.0)
Nonneutropenic	28/32 (87.5)
Baseline pathogen	
C albicans	11/13 (84.6)
C glabrata	4/4 (100)
C guilliermondii	1/1 (100)
C krusei	0/1 (0.0)
C lambica	2/2 (100)
C lusitaniae[b]	3/3 (100)
C parapsilosis[b]	7/8 (87.5)
C tropicalis	2/5 (40.0)

n/N indicates the number of patients with a favorable response/number of patients in the subgroup.

[a] Data show the complete and partial responses combined.

[b] One patient had both *C lusitaniae* and *C parapsilosis* identified at the study site but was only identified as having a baseline pathogen attributed to *C lusitaniae* by the central microbiological laboratory.

Safety and Tolerability

Among all 49 of the patients, 13 (27%) had ≥1 clinical adverse event considered at least possibly related to caspofungin therapy by the investigator (Table 3). None of the drug-related clinical adverse events were considered serious or resulted in discontinuation of caspofungin therapy. The most common drug-related clinical adverse events were fever (3 patients [6%]) and rash (2 patients [4%]). Five patients (10%) died during the study; all 5 were being treated for invasive aspergillosis. None of the deaths were related to caspofungin therapy, as determined by the investigator (4 were attributed to underlying disease or its complications and 1 to fungal infection).

Seventeen (35%) of the 49 patients had ≥1 laboratory adverse event that was determined by the investigator to be at least possibly related to caspofungin therapy (Table 3). None of these events were serious or led to therapy interruption or discontinuation. The most common drug-related laboratory adverse events were elevated liver transaminases in 10 patients (3 with increased AST, 1 with increased ALT, and 6 with elevations in both enzymes). These elevations were ≤2 times the ULN in 6 patients, <5 times ULN in 3, and >5 times ULN in 1. In 8 of these 10 patients (including the patient with levels >5 times ULN), the elevations resolved or returned to baseline levels during caspofungin therapy or during the 14-day follow-up period. In the remaining 2 patients, elevated AST/ALT was noted only after completion of caspofungin therapy, and no additional samples were available for evaluation.

Local and systemic tolerability to caspofungin were assessed each day during caspofungin infusion and for 1 hour after infusion. At the end of caspofungin therapy, the overall local tolerability rating was "well tolerated" in 46 patients (94%) and "moderately well tolerated" in 3 (6%). Four patients (8%) had local reactions attributed to caspofungin infusion. These reactions were generally mild and transient and included itching/hives, pain/swelling, and redness at the infusion site in 1 patient (2%) each. The fourth patient developed severe thrombophlebitis while receiving caspofungin via a peripheral line using a reduced volume (as permitted by the protocol on the first 2 days of therapy); the infusion volume was increased to 100 mL from day 3 forward with no additional local tolerability issues.

Forty-one (84%) of the 49 patients had an overall systemic tolerability rating of "no infusion-related events" at the end of caspofungin therapy. Eight patients (16%) experienced ≥1 systemic infusion-related event. These included fever in 4 patients (8%) and chills, hypotension, oxygen saturation decreased, and maculopapular rash in 1 patient (2%) each. None of these events led to therapy discontinuation, and all but 1 (moderate fever) were mild and transient.

Dose Escalation

The caspofungin dosage was increased because of inadequate response (as judged by the investigator) in 1 patient with invasive aspergillosis and 4 patients with candidemia. Three of the patients with candidemia had a complete response at the end of caspofungin therapy. The remaining patient with candidemia and the patient with invasive aspergillosis had an unfavorable response after 1 and 3 days, respectively, of the higher-dose regimen; study therapy was then discontinued because of poor prognosis. No safety concerns of clinical significance were noted in these patients, including 1 who received caspofungin 70 mg/m^2 per day for 36 days.

DISCUSSION

We found that caspofungin was well tolerated and effective in children with documented *Candida* or *Aspergillus* infections. This study was primarily intended to assess the safety of caspofungin in pediatric patients; however, efficacy was also assessed. Efforts were made to design the study as closely as possible to the previous studies in adults[17–20] with regard to diagnostic criteria,[22] as well as efficacy time points and end points. A noncomparative design was used in this study to maximize the experience for caspofungin; because the identification and inclusion of such patients in a prospective clinical trial are very challenging because of the severity of the patients' underlying medical conditions and the difficulties encountered in confirming the diagnosis of invasive fungal infections. The sample size was based on logistic considerations, as noted above, and not statistical considerations. Although the noncomparative design and the small sample size limit the interpretation of the

data, the results from this study provide important clinical information on the use of caspofungin in the treatment of important fungal infections in the pediatric population.

Caspofungin was generally well tolerated in this study. Drug-related clinical and laboratory adverse events, the primary safety end point of the study, occurred in 26.5% and 34.7% of patients, respectively. These are generally similar to the incidence rates seen in adults.[17–20] Most drug-related clinical adverse events were mild, and none led to therapy discontinuation. The most common drug-related laboratory adverse event was an increased hepatic transaminase level, which often occurred in the setting of other medical conditions and/or concomitant therapies that could have contributed to the elevation. None of the drug-related laboratory adverse events led to therapy interruption or discontinuation.

The 50% favorable response rate in children with invasive aspergillosis in this study is similar to the favorable response rate found in adults (48%) receiving caspofungin 50 mg/day.[17] This response rate is not unexpected, because patients were not enrolled unless they were refractory or intolerant to previous antifungal therapy. Similar response rates have been observed in prospective studies of children receiving voriconazole (43%)[27] or amphotericin B lipid complex (ABLC) for invasive aspergillosis (56%).[28] Retrospective studies of ABLC have found response rates ranging from 39%[29] to 78%[30] in children with invasive aspergillosis. Most patients in our study had pulmonary aspergillosis. One patient had CNS aspergillosis and had a favorable response to caspofungin, but this result should be interpreted with caution, because experience with caspofungin in CNS infection is limited. Despite aggressive medical and surgical management, mortality for invasive aspergillosis in children with cancer can be as high as 85% in the first year after diagnosis.[14,31] In the current study, 5 (50%) of the 10 patients with invasive aspergillosis died during the study, which is similar to the 41% mortality rate in children with invasive aspergillosis treated with voriconazole.[27]

The 81% overall response rate in children with invasive candidiasis in this study is similar to the response rate in adults (~74%–81%).[19,20] Most of the children (82%) in this study received caspofungin as primary therapy; however, 5 (71%) of 7 patients receiving salvage therapy also had a favorable response. These response rates are similar to those reported for ABLC in children with invasive candidiasis refractory to previous therapy: 81% in a prospective, emergency-use study[28] and 58% to 89% in retrospective studies.[29,30] In our study, there were no differences in the effectiveness of caspofungin by the site of *Candida* infection, *Candida* species, or patient age; however, the small number of patients in each subgroup limits the interpretation of these results.

CONCLUSIONS

Caspofungin 50 mg/m^2 per day (maximum: 70 mg/day; after 70 mg/m^2 on day 1) was generally well tolerated in children 6 months to 17 years of age. Efficacy outcomes in patients with invasive aspergillosis and invasive candidiasis were consistent with those reported previously in adults receiving caspofungin[17–20] and in children receiving other antifungal therapies.[27–30] Caspofungin seems to provide an effective, well-tolerated alternative for the treatment of *Candida* and *Aspergillus* infections in pediatric patients.

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