MAJOR ARTICLE

A Multicenter, Double-Blind Trial of a High-Dose Caspofungin Treatment Regimen versus a Standard Caspofungin Treatment Regimen for Adult Patients with Invasive Candidiasis

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Background. The standard caspofungin treatment regimen (50 mg/day after a 70-mg dose on day 1) is effective and well tolerated for the treatment of invasive candidiasis, but experience with higher doses of caspofungin is limited. We evaluated the safety and efficacy of caspofungin at 3 times the standard dosing regimen.

Methods. Patients with proven invasive candidiasis were randomized to receive a standard or high-dose (150 mg/day) caspofungin treatment regimen. Safety was assessed in all patients as treated. Efficacy was assessed as a secondary objective in a full-analysis-set population. A favorable overall response was defined as symptom resolution and microbiological clearance at the end of caspofungin therapy.

Results. A total of 204 patients were included in the safety analysis (104 received the standard regimen, and 100 received the high-dose regimen), and 197 were included in the efficacy analysis (102 and 95 in the standard and high-dose treatment groups, respectively). Patient demographic characteristics, neutropenia status (6.7% and 8.0% had neutropenia, respectively), and Acute Physiology and Chronic Health Evaluation II scores (mean, 16.5 and 17, respectively) were similar between treatment groups. Significant drug-related adverse events occurred in 1.9% of patients receiving the standard regimen and 3.0% of patients receiving the high-dose regimen (difference, 1.1%; 95% confidence interval, −4.1% to 6.8%). The most-common drug-related adverse events in the standard and high-dose treatment groups were phlebitis (3.8% and 2.0%, respectively), increased alkaline phosphatase level (6.9% and 2.0%, respectively), and increased aspartate transaminase level (4.0% and 2.0%, respectively). Overall, 71.6% of patients who received the standard regimen and 77.9% of patients who received the high-dose regimen had favorable overall responses (difference, 6.3%; 95% confidence interval, −5.9% to 18.4%; not statistically significant). Mortality at 8 weeks after therapy was similar between groups.

Conclusions. Both caspofungin dosing regimens were effective and well tolerated in patients with invasive candidiasis. No safety concerns were found for caspofungin at a dosage of 150 mg/day.

The incidence and clinical importance of serious *Candida* infections have increased dramatically during the past 20 years [1, 2]. *Candida* species currently represent the fourth-most common organisms in nosocomial bloodstream infections and the sixth-most common nosocomial pathogens overall [1]. Mortality among patients with invasive candidiasis is 3 times higher than that among control individuals, with an attributable mortality of ~30% [3, 4].

Caspofungin is a parenteral echinocandin antifungal

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[a] Members of the study group are listed at the end of the text.

agent that has fungicidal activity against *Candida* species [5]. Prior studies have demonstrated that caspofungin at a dosage of 50 mg/day (after a 70-mg loading dose on day 1 of treatment) is as effective as amphotericin B deoxycholate for the treatment of invasive candidiasis [6]. Although doses as high as 2 times the standard dose have been administered to humans [5], the efficacy and safety of caspofungin at higher doses have not been fully characterized. Therefore, we compared the standard caspofungin regimen with a higher-dose caspofungin regimen (150 mg/day) in patients with invasive candidiasis.

METHODS

This was a multicenter, randomized, double-blind study conducted from January 2006 through January 2008 at 38 sites in North and South America, Europe, and Asia to evaluate the safety, tolerability, and efficacy of caspofungin at a dosage of 50 mg/day (after a 70-mg loading dose on day 1 of treatment), compared with caspofungin at a dosage of 150 mg/day, in the first-line treatment of adults with invasive candidiasis. The protocol was approved by the institutional review board or ethics review committee at each site, and written informed consent was obtained from each patient before any study procedures were performed. An independent data and safety monitoring board monitored the accumulating safety data of the study.

Patient selection. Adult patients (age, ⩾18 years) were eligible for inclusion if they had both clinical and microbiological evidence of invasive candidiasis at a sterile site, in accordance with the criteria for proven invasive candidiasis described by the Mycosis Study Group and the European Organization for the Research and Treatment of Cancer [7]. Additional selection criteria were as described elsewhere [6].

Study design. Patients were randomly assigned in a 1:1 ratio to receive caspofungin at a dosage of 50 mg/day after a 70-mg dose on day 1 of treatment (hereafter, referred to as the "70/50-mg treatment group") or caspofungin at a dosage of 150 mg/day without a loading dose (hereafter, referred to as the "150-mg treatment group") according to a computer-generated allocation schedule. Caspofungin was administered over ~2 h as a single daily dose. The duration of antifungal therapy followed the treatment guidelines set forth by the Infectious Diseases Society of America [8]. Patients were to be treated for ⩾14 days after both improvement in clinical and radiographical signs of disease and the eradication of *Candida* species from culture samples obtained from the invasive site of infection. After ⩾10 days of caspofungin therapy, patients either continued to receive caspofungin therapy or were switched to receive oral fluconazole therapy at doses ⩾400 mg/day. Fluconazole therapy could only be given if 48 h had elapsed since the last positive culture, there was a significant decrease in the signs and symptoms of infection, the patient was not neutropenic, and the *Candida* species was found to be susceptible to fluconazole (minimum inhibitory concentration, ⩽8 μg/mL). Patients with infection caused by *Candida krusei* or *Candida glabrata* continued to receive caspofungin therapy. Clinical signs and symptoms were assessed daily while patients received caspofungin therapy, twice weekly while they received oral antifungal therapy, and at 2 and 8 weeks after completion of all antifungal therapy. Follow-up procedures were as described elsewhere [6].

Safety and efficacy evaluation. Patients were monitored daily for adverse events while they received caspofungin therapy and for 14 days thereafter. The primary safety measure was the proportion of patients who developed a significant drug-related adverse event, which was defined as a drug-related adverse event that was serious or that led to discontinuation of caspofungin treatment. Adverse events are common in patients with invasive *Candida* infection, because these patients have serious underlying medical conditions and receive multiple concomitant medications. Therefore, drug-related adverse events, rather than all adverse events, were chosen for the primary safety evaluation, to allow for a more accurate assessment of the caspofungin safety profile.

The main efficacy parameter was the overall (clinical and microbiological) response. A favorable overall response required resolution of all symptoms and signs of *Candida* infection and culture-confirmed *Candida* eradication (or presumptive eradication for nonblood sites of infection). Evaluations were performed on day 10 of caspofungin therapy, at the end of caspofungin therapy, and at the end of all antifungal therapy (accounting for the potential switch to oral fluconazole treatment). The main assessment of efficacy was predefined as the end of caspofungin therapy. Patients who had a favorable overall response at both the end of caspofungin therapy and the end of all antifungal therapy were counted as having a relapse if there was recurrence of cultures positive for *Candida* species or if the patient received systemic antifungal therapy for a proven or suspected *Candida* infection during the follow-up period.

Statistical methods. The primary hypothesis was that the high-dose regimen would be noninferior to the standard regimen with respect to the development of significant drug-related adverse events; noninferiority was defined such that the upper limit of the 2-sided 95% confidence interval (CI) for the treatment-group difference in the percentage of patients with significant drug-related adverse events must be <15%. With a planned sample size of 100 patients per treatment group and under the assumption of a 3.5% incidence for each group, the study was planned to have 99% power to detect noninferiority. An all-patients-as-treated approach was used for the safety analysis.

Efficacy was predefined as a secondary objective, because the study was not sufficiently powered to confirm noninferiority

Table 1. Patient characteristics at baseline.

Characteristic	Caspofungin 70/50-mg group (n = 104)	Caspofungin 150-mg group (n = 100)
Sex		
Male	54 (51.9)	60 (60.0)
Female	50 (48.1)	40 (40.0)
Race		
White	70 (67.3)	65 (65.0)
Black	11 (10.6)	12 (12.0)
Asian	17 (16.3)	16 (16.0)
Other	6 (5.8)	7 (7.0)
Age, years		
Mean ± SD	56.0 ± 18.0	57.8 ± 16.8
Median (range)	57.5 (16–90)	61.0 (20–87)
APACHE II score at study entry[a]		
⩽20	77 (74.0)	72 (72.0)
>20	26 (25.0)	27 (27.0)
Mean ± SD	16.5 ± 8.2	17.0 ± 7.6
Median (range)	16.0 (3–38)	16.0 (2–39)
Neutropenia status at study entry		
ANC ⩾500 cells/μL	97 (93.3)	92 (92.0)
ANC <500 cells/μL	7 (6.7)	8 (8.0)
Risk factor[b]		
Active malignancy	27 (26.0)	33 (33.0)
Broad-spectrum antibiotic therapy	76 (73.1)	86 (86.0)
Diabetes mellitus	31 (29.8)	28 (28.0)
Immunosuppression	29 (27.9)	29 (29.0)
Major surgery	49 (47.1)	43 (43.0)
Total parenteral nutrition	37 (35.6)	41 (41.0)
Transplant recipient	6 (5.8)	4 (4.0)
Trauma	7 (6.7)	5 (5.0)
Other	11 (10.6)	11 (11.0)
Site of infection		
Abscess	…	3 (3.0)
Blood	91 (87.5)	81 (81.0)
Peritoneal fluid	4 (3.8)	5 (5.0)
Acute disseminated/multiple sites[c]	6 (5.8)	7 (7.0)
Other[d]	3 (2.9)	4 (4.0)
Prior antifungal therapy		
No	48 (46.2)	51 (51.0)
Yes	56 (53.8)	49 (49.0)

NOTE. Data are no. (%) of patients, unless otherwise specified. ANC, absolute neutrophil count; APACHE, Acute Physiology and Chronic Health Evaluation; caspofungin 70/50-mg group, group who received caspofungin at a dosage of 50 mg/day after a 70-mg loading dose on day 1 of treatment; caspofungin 150-mg group, group who received caspofungin at a dosage of 150 mg/day.

[a] One patient in each treatment group did not have APACHE II scores measured at study entry.

[b] Some patients are in >1 risk category.

[c] Multiple sites include candidemia in all 13 patients, along with *Candida* endophthalmitis (2 patients in the caspofungin 70/50-mg group and 5 patients in the caspofungin 150-mg group), *Candida* peritonitis (3 and 2 patients, respectively), or *Candida* empyema (1 patient in the caspofungin 70/50-mg group).

[d] Other includes 2 patients with suspected *Candida* pneumonia (1 in each treatment group), 2 patients with non-*Candida* fungemia (both in the caspofungin 150-mg group), 1 patient with *Candida* empyema (caspofungin 70/50-mg group), 1 patient with *Candida* pyelonephritis (caspofungin 150-mg group) and 1 patient with chronic disseminated candidiasis (caspofungin 70/50-mg group).

Table 2. *Candida* species isolates at baseline.

Candida species isolated	Isolates, %	
	Caspofungin 70/50-mg group	Caspofungin 150-mg group
C. albicans	41.5	41.9
C. parapsilosis	19.1	22.6
C. tropicalis	19.1	17.2
C. glabrata	9.6	9.7
C. guilliermondii	3.2	1.1
C. krusei	0	2.2
C. lusitaniae	1.1	1.1
C. rugosa	0	1.1
Multiple species[a]	6.4	3.2

NOTE. Caspofungin 70/50-mg group, group who received caspofungin at a dosage of 50 mg/day after a 70-mg loading dose on day 1 of treatment; caspofungin 150-mg group, group who received caspofungin at a dosage of 150 mg/day.

[a] In the caspofungin 70/50-mg group, there were 3 patients with *C. albicans* and *C. glabrata,* 1 patient with *C. albicans* and *C. tropicalis,* 1 patient with *C. albicans* and *C. parapsilosis,* and 1 patient with *C. fatama* and *C. intermedia.* In the caspofungin 150-mg group, there were 2 patients with *C. albicans* and *C. tropicalis,* and 1 patient with *C. albicans* and *C. glabrata.*

or superiority between treatment groups. No formal hypothesis testing for efficacy was performed. Efficacy was evaluated in a full-analysis-set population, which included patients with a documented diagnosis of invasive candidiasis who received ⩾1 dose of caspofungin.

RESULTS

Baseline characteristics. A total of 104 patients in the 70/50-mg treatment group and 100 patients in the 150-mg treatment group were included in the all-patients-as-treated population. The 2 treatment groups were similar at study entry with regard to age, race, sex, risk factors, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and neutropenia status (table 1). In total, 87.5% of patients in the 70/50-mg treatment group and 81.0% in the 150-mg treatment group had candidemia. The number of patients with other sites of infection was similar between treatment groups. Approximately 50% of patients in both treatment groups received prior antifungal therapy, the duration of which was limited to 1 day in most cases. Fluconazole was the most commonly administered antifungal agent in the prestudy period. The most common infecting *Candida* pathogen in both treatment groups was *Candida albicans* (table 2).

Treatment duration. The mean duration of caspofungin therapy was almost identical for the 2 treatment groups (14.5 days [range, 1–49 days] for the 70/50-mg treatment group and 14.2 days [range, 1–51 days] for the 150-mg treatment group). A switch to oral fluconazole therapy after ⩾10 days of caspofungin therapy occurred for 33 (16.2%) of the 204 patients: 15 (14.4%) of 104 patients in the 70/50-mg treatment group and 18 (18.0%) of 100 patients in the 150-mg treatment group.

Table 3. Safety outcomes.

Outcome	Caspofungin 70/50-mg group (n = 104)	Caspofungin 150-mg group (n = 100)	Observed difference,[a] % (95% confidence interval)
Drug-related adverse events[b]			
Significant[c]	2 (1.9) [0.2–6.8]	3 (3.0) [0.6–8.5]	1.1 (−4.1 to 6.8)
Serious	0 (0.0) [0.0–3.5]	3 (3.0) [0.6–8.5]	3.0 (−0.6 to 8.5)
Leading to discontinuation of caspofungin therapy	2 (1.9) [0.2–6.8]	2 (2.0) [0.2–7.0]	0.1 (−5.0 to 5.3)
All	20 (19.2) [12.2–28.1]	19 (19.0) [11.8–28.1]	−0.2 (−11.1 to 10.8)
Most common			
Phlebitis	4 (3.8)	2 (2.0)	…
Alkaline phosphatase increased	7/101 (6.9)	2/98 (2.0)	…
AST increased	4/101 (4.0)	2/99 (2.0)	…
ALT increased	2/101 (2.0)	2/99 (2.0)	…
Adverse events irrespective of investigator-determined causality			
Clinical	83 (79.8)	80 (80.0)	…
Serious clinical	46 (44.2)	44 (44.0)	…
Laboratory	29 (28.4)	35 (35.4)	…
Serious laboratory	1 (1.0)	1 (1.0)	…

NOTE. Data are no. (%) of patients with ⩾1 of specified event [95% confidence interval for the percentage of patients] or no. of patients with ⩾1 of specified event/no. of patients with the laboratory test result recorded during caspofungin therapy (%), unless otherwise specified. ALT, alanine aminotransferase; AST, aspartate aminotransferase; caspofungin 70/50-mg group, group who received caspofungin at a dosage of 50 mg/day after a 70-mg loading dose on day 1 of treatment; caspofungin 150-mg group, group who received caspofungin at a dosage of 150 mg/day.

[a] Caspofungin 150-mg group minus caspofungin 70/50-mg group. Calculated for drug-related adverse event categories only; there were no statistically significant differences between treatment groups.

[b] Clinical or laboratory adverse events determined by the investigator to be possibly, probably, or definitely related to the study therapy.

[c] Drug-related adverse events that were serious or that led to discontinuation of caspofungin therapy.

Table 4. Efficacy outcomes.

Outcome	Caspofungin 70/50-mg group (n = 102)	Caspofungin 150-mg group (n = 95)	Observed difference,[a] % (95% confidence interval)
At end of caspofungin therapy			
Favorable overall response	73/102 (71.6) [61.8–80.1]	74/95 (77.9) [68.2–85.8]	6.3 (−5.9 to 18.4)
Favorable clinical response	73/102 (71.6) [61.8–80.1]	76/95 (80.0) [70.5–87.5]	8.4 (−3.7 to 20.3)
Favorable microbiological response	84/102 (82.4) [73.6–89.2]	84/95 (88.4) [80.2–94.1]	6.1 (−4.0 to 16.2)
At day 10 of caspofungin therapy[b]: favorable overall response	68/81 (84.0) [74.1–91.2]	69/73 (94.5) [86.6–98.5]	10.6 (0.7 to 20.9)
At end of all antifungal therapy: favorable overall response	72/102 (70.6) [60.7–79.2]	74/95 (77.9) [68.2–85.8]	7.3 (−5.0 to 19.4)
Relapse assessments			
Relapse at 2 weeks after therapy	5/61 (8.2) [2.7–18.1]	1/58 (1.7) [0.0–9.2]	−6.5 (−16.4 to 1.9)
Relapse at 8 weeks after therapy	7/61 (11.5) [4.7–22.2]	1/58 (1.7) [0.0–9.2]	−9.8 (−20.4 to −0.9)

NOTE. Data are no. of patients with a favorable response/no. of patients in the subgroup (%) [95% confidence interval], unless otherwise specified. There were no statistically significant differences between the treatment groups except for the day 10 analysis. Caspofungin 70/50-mg group, group who received caspofungin at a dosage of 50 mg/day after a 70-mg loading dose on day 1 of treatment; caspofungin 150-mg group, group who received caspofungin at a dosage of 150 mg/day.

[a] Caspofungin 150-mg group minus caspofungin 70/50-mg group.

[b] The efficacy analysis on day 10 of caspofungin therapy was calculated only for those patients who received at least 10 days of caspofungin therapy. If all the patients who were excluded from the day 10 analysis are counted as having unfavorable responses, then the overall responses on day 10 of therapy would be similar between the treatment groups: 68 (66.7%) of 102 patients in the caspofungin 70/50-mg group and and 69 (72.6%) of 95 patients in the caspofungin 150-mg group.

The median duration of oral fluconazole therapy was similar for the 70/50-mg and 150-mg treatment groups (6.0 and 5.5 days, respectively).

Safety and tolerability. Significant drug-related adverse events were reported for 2 patients (1.9%) in the 70/50-mg treatment group and 3 patients (3.0%) in the 150-mg treatment group (table 3). The observed difference between the treatment groups was 1.1%, with a 95% CI of −4.1 to 6.8, which fulfilled the predefined criterion for noninferiority. The incidences of drug-related clinical adverse events (13.5% vs. 14.0%), serious drug-related clinical adverse events (0% vs. 3.0%), and discontinuations of caspofungin therapy because of drug-related clinical adverse events (1.9% vs. 2.0%) were similar between the 70/50-mg and 150-mg treatment groups, respectively. Only 1 specific drug-related clinical adverse event (injection-site phlebitis) was reported in >2 patients in either treatment group (3.8% and 2.0% of patients in the 70/50-mg and 150-mg treatment groups, respectively). Among 201 patients with postbaseline laboratory test results, drug-related laboratory adverse events occurred in 7.8% of the 70/50-mg treatment group and 7.1% of the 150-mg treatment group. The most-common drug-related laboratory adverse events in both treatment groups were increased aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels (table 3). None of the drug-related laboratory events were serious or led to discontinuation of caspofungin treatment. The overall rates of clinical and laboratory adverse events, regardless of causality, were also similar between the treatment groups (table 3).

Efficacy. Overall, 197 of the 204 patients included in the all-patients-as-treated population were also included in the full-analysis-set population (102 in the 70/50-mg treatment group and 95 in the 150-mg treatment group). At the end of caspofungin therapy, 71.6% of patients in the 70/50-mg treatment group and 77.9% of patients in the 150-mg treatment group had a favorable overall response (table 4). A favorable clinical response occurred for 71.6% of the 70/50-mg treatment group and 80.0% of patients in the 150-mg treatment group. A favorable microbiological response occurred for 82.4% of patients in the 70/50-mg treatment group and 88.4% of patients in the 150-mg treatment group. For each response category, there were no statistically significant differences between the treatment groups.

More patients in the 70/50-mg treatment group than in the 150-mg treatment group had cultures persistently positive for *Candida* species associated with an unfavorable overall response (11.8% vs. 3.2%, respectively), but this difference was not statistically significant. The 70/50-mg and 150-mg treatment groups were similar with regard to the percentage of patients with persistently positive signs and/or symptoms of *Candida* infection (4.9% vs. 5.3%, respectively), treatment discontinuations because of drug-related adverse events (1.0% vs. 2.1%, respectively), evidence of new *Candida* lesions at distant sites (1.0% vs. 0%, respectively), and indeterminate assessments (9.8% vs. 11.6%, respectively). In both treatment groups, most cases with persistently positive cultures were due to *C. albicans* (5 and 2 cases in the 70/50-mg and 150-mg treatment groups, respectively) and *Candida parapsilosis* (5 cases and 1 case, respectively). Failure at the end of caspofungin therapy was not correlated with increasing minimum inhibitory concentration to caspofungin for the follow-up isolates.

Trends similar to those seen at the end of caspofungin therapy were noted on day 10 of treatment and at the end of all

Table 5. Overall response rates, by specific underlying factors.

Factor	Caspofungin 70/50-mg group ($n = 102$)	Caspofungin 150-mg group ($n = 95$)
Single site of *Candida* infection		
Blood (candidemia)	67/91 (73.6)	62/79 (78.5)
Abscess	…	3/3 (100)
Peritoneal fluid	3/4 (75.0)	5/5 (100)
Pleural fluid	1/1 (100)	…
Chronic disseminated (hepatosplenic)	0/1 (0)	…
Urine (pyelonephritis)	…	1/1 (100)
Multiple sites of *Candida* infection		
Blood and eye (endophthalmitis)	0/2 (0)	3/5 (60.0)
Blood and peritoneal fluid	2/2 (100)	0/2 (0)
Blood and pleural fluid	0/1 (0)	…
APACHE II score at entry		
⩽20	56/76 (73.7)	54/68 (79.4)
>20	16/25 (64.0)	19/26 (73.1)
Neutropenia status at entry		
Nonneutropenic	71/96 (74.0)	70/88 (79.5)
Neutropenic	2/6 (33.3)	4/7 (57.1)
Baseline *Candida* species isolate		
C. albicans	27/39 (69.2)	32/39 (82.1)
C. glabrata	8/9 (88.9)	7/9 (77.8)
C. guilliermondii	2/3 (66.7)	1/1 (100)
C. krusei	…	1/2 (50.0)
C. lusitaniae	1/1 (100)	1/1 (100)
C. parapsilosis	11/18 (61.1)	17/21 (81.0)
C. rugosa	…	1/1 (100)
C. tropicalis	13/18 (72.2)	9/16 (56.3)
Non–*C. albicans*	35/49 (71.4)	37/51 (72.5)
Mixed infection[a]	5/6 (83.3)	3/3 (100)

NOTE. Data are no. of patients with a favorable response/no. of patients in the subgroup (%). APACHE, Acute Physiology and Chronic Health Evaluation; caspofungin 70/50-mg group, group who received caspofungin at a dosage of 50 mg/day after a 70-mg loading dose on day 1 of treatment; caspofungin 150-mg group, group who received caspofungin at a dosage of 150 mg/day.

[a] In the caspofungin 70/50-mg group, favorable responses were seen in 2 of 3 patients with *C. albicans* and *C. glabrata* infection, 1 patient with *C. albicans* and *C. tropicalis* infection, 1 patient with *C. albicans* and *C. parapsilosis* infection, and 1 patient with *C. famata* and *C. intermedia* infection. In the caspofungin 150-mg group, favorable responses were seen in 2 patients with *C. albicans* and *C. tropicalis* infection and 1 patient with *C. albicans* and *C. glabrata* infection.

antifungal therapy (table 4). Notably, the rates of favorable overall response at the end of all antifungal therapy were very similar to those observed at the end of caspofungin therapy. Of the 119 patients who had a favorable overall response at the end of caspofungin therapy and were followed up long enough to assess for relapse, 5 (8.2%) of 61 patients in the 70/50-mg treatment group and 1 (1.7%) of 58 patients in the 150-mg treatment group had a relapse at 2 weeks after therapy. By 8 weeks after therapy, relapse had occurred for 7 (11.5%) of 61 patients in the 70/50-mg treatment group and in 1 (1.7%) of 58 patients in the 150-mg treatment group. All relapses in this study were microbiological relapses, and most were also considered to be clinical relapses. Five patients (4 in the 70/50-mg treatment group and 1 in the 150-mg treatment group) had *Candida* species identified at the time of relapse that were different from those identified at initial presentation, which suggests the development of new infections.

Efficacy by underlying factors. The rates of favorable overall response for the different sites of *Candida* infection were generally similar between the treatment groups (table 5). Among patients with candidemia, 73.6% of those in the 70/50-mg treatment group and 78.5% of those in the 150-mg treatment group had a favorable overall response. In both treatment groups, patients with *Candida* peritonitis also responded favorably. Favorable responses were seen for all sites of *Candida* infection except chronic disseminated candidiasis (i.e., the 1 patient with hepatosplenic involvement had an indeterminate efficacy evaluation at the end of caspofungin therapy). Approximately 40% of the patients in both treatment groups with multiple sites of *Candida* infection had a favorable overall response at the end of caspofungin therapy. In addition, 3 of the 5 patients in the 150-mg treatment group who had candidemia and candidal endophthalmitis had a favorable overall response at the end of caspofungin therapy, whereas neither of the 2 patients in the 70/50-mg treatment group with candidemia and candidal endophthalmitis had a favorable response.

In patients with candidemia, the impact of central venous catheter (CVC) management and the time to negative results of blood cultures were also assessed. Overall, there were no differences between the treatment groups on the basis of CVC management during the prestudy period (table 6). Many patients with candidemia had a CVC in place within 14 days before enrollment, but 103 of the 182 patients (56 in the 70/

Table 6. Overall response rates by retention or removal of a central venous catheter or peripheral-inserted central catheter (CVC) in patients with candidemia.

Status[a]	Caspofungin 70/50-mg group ($n = 96$)	Caspofungin 150-mg group ($n = 86$)
No CVC in place	29/40 (72.5)	29/39 (74.4)
CVC in place		
CVC removed or changed prestudy	22/29 (75.9)	17/23 (73.9)
CVC removed prestudy	17/23 (73.9)	15/19 (78.9)
CVC changed prestudy	5/6 (83.3)	2/4 (50.0)
CVC not removed or changed prestudy	18/27 (66.7)	19/24 (79.2)

NOTE. Data are no. of patients with a favorable response/no. of patients in the subgroup (%). Caspofungin 70/50-mg group, group who received caspofungin at a dosage of 50 mg/day after a 70-mg loading dose on day 1 of treatment; caspofungin 150-mg group, group who received caspofungin at a dosage of 150 mg/day.

[a] "Removed" signifies that CVC was completely removed. "Changed" indicates that the CVC was changed over a wire but was maintained in the same location.

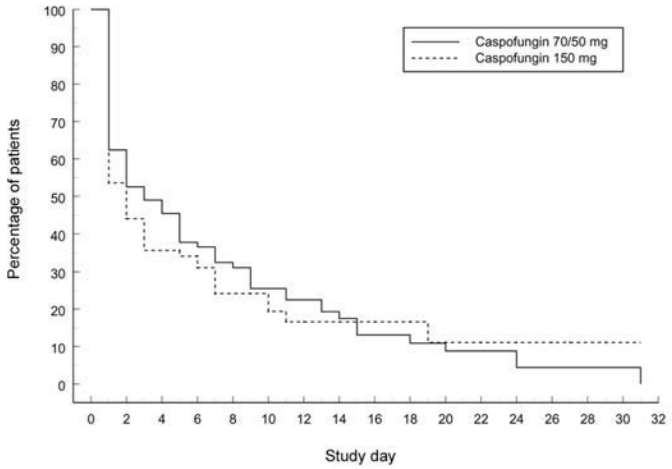

Figure 1. Kaplan-Meier analysis of the time to clearance of blood cultures in patients with candidemia. The log-rank χ^2 statistic was not significant ($P = .47$), thereby suggesting no difference between treatment groups with respect to time to achievement of a negative blood culture among all patients with candidemia. The 2 treatment regimens were caspofungin at a dosage of 50 mg/day after a 70-mg dose on day 1 and caspofungin at a dosage of 150 mg/day.

50-mg treatment group and 47 in the 150-mg treatment group) had a CVC in place on the day that the first blood culture specimen positive for *Candida* species was obtained. Success rates in both treatment groups for patients with a CVC in place (71.4% and 76.6% in the 70/50-mg and 150-mg treatment groups, respectively) were comparable to the results in patients with no CVC in place at the time that the first positive culture specimen was obtained (72.5% and 74.4%, respectively). For patients with a CVC in place before the study, efficacy results did not vary significantly in either treatment group on the basis of whether they had their CVCs removed or changed during the prestudy period. In addition, there was no marked difference between the treatment groups in the time to achievement of a negative blood culture. A Kaplan-Meier analysis of the proportion of patients with a positive blood culture during the period of study therapy (figure 1) demonstrated that the log-rank χ^2 statistic was not significant ($P = .47$), suggesting no difference between treatment groups with respect to time to achievement of a negative blood culture.

Rates of favorable overall response were generally comparable between treatment groups for each category of APACHE II scores and for nonneutropenic patients (table 5). In each treatment group, the proportion of patients with a favorable overall response was numerically lower in the subgroup with APACHE II scores >20 and in neutropenic patients; however, the number of neutropenic patients in each treatment group was small. Favorable responses were noted for infections with all *Candida* species (table 5), although the direction of the response was inconsistent from one pathogen to another. For patients infected with *C. albicans* or *C. parapsilosis,* rates of favorable overall response were numerically higher in the 150-mg treatment group; for patients infected with *Candida tropicalis* or *C. glabrata,* rates of favorable overall response were numerically higher in the 70/50-mg treatment group. These differences between treatment groups were not statistically significant. Overall, the response across infections with all non–*C. albicans* species was similar between the 70/50-mg and 150-mg treatment groups (35 [71.4%] of 49 patients vs. 37 [72.5%] of 51 patients, respectively).

Mortality. Deaths while receiving study therapy or during the 8 weeks after therapy were evenly distributed between the treatment groups: 33.7% of patients in the 70/50-mg treatment group and 38.0% of patients in the 150-mg treatment group. Within the first 10 days of caspofungin therapy, death occurred for 11.5% of patients in the 70/50-mg treatment group and 17.0% of patients in the 150-mg treatment group. Most of the deaths represented complications of the patients' underlying medical conditions. None were considered by the investigator to be related to caspofungin therapy.

DISCUSSION

We used a randomized, double-blind study design to characterize the safety and efficacy of caspofungin at a dosage 3 times higher (150 mg/day) than the currently licensed standard dosage (50 mg/day after 70-mg on day 1 of treatment). The diagnostic criteria, efficacy time points, and end points used in this study mirrored those used in the pivotal study of caspofungin versus amphotericin B for treatment of invasive candidiasis [6]. The maximum tolerated dose of caspofungin remains unknown. In a phase I study, single doses of up to 210 mg were well tolerated in healthy subjects [9]. Furthermore,

caspofungin at a dosage of 100 mg/day was well tolerated in patients with invasive aspergillosis [10] or invasive candidiasis [11], with no reports of serious drug-related adverse events or discontinuations of study therapy because of drug-related adverse events. Similar safety results have been reported for marketed caspofungin at a dosage of 100 mg/day [12]. Because multiple-dose data for dosages >100 mg/day were not available, we chose to consider an even higher dose (i.e., 150 mg/day) for evaluation in the current study involving patients with an appropriate clinical risk-to-benefit ratio.

Overall, caspofungin treatment was generally well tolerated at both dosages studied. The incidence of significant drug-related adverse events was low in both treatment groups. The incidence of serious drug-related adverse events was also low, and few patients had to discontinue caspofungin therapy because of a drug-related adverse event. The pattern of specific drug-related clinical or laboratory adverse events in both treatment groups was similar to that reported previously for caspofungin-treated adults with invasive candidiasis [6, 11]. Overall, no new safety concerns were identified in the review of clinical and laboratory safety data for the higher-than-approved dose of caspofungin.

This study was not sufficiently powered to confirm either noninferiority or superiority for efficacy between the treatment groups. Nevertheless, the proportion of patients with a favorable overall response at the end of caspofungin therapy was similar between treatment groups. In general, the outcome was consistent across a variety of key prognostic factors, without a definitive demonstration of an efficacy benefit for one particular treatment group. Although there were numerical trends favoring the 150-mg treatment group for certain analyses (e.g., analysis of patients with *C. parapsilosis* infection), these differences were not statistically significant and must be viewed accordingly. Furthermore, the mortality rates during caspofungin therapy and the 8-week follow-up period were similar between treatment groups.

The rate of favorable overall response for the 70/50-mg treatment group in the current study (72%) was nearly identical to the response rate for the 70/50-mg treatment group (73%) in the prior study of caspofungin versus amphotericin B deoxycholate [6]. These results compare favorably to the 62% response rate seen for amphotericin B deoxycholate treatment in the prior study [6] and to the success rates found across all treatment groups (73%–76%) in a study comparing the standard caspofungin treatment regimen with micafungin therapy at dosages of 100 mg/day and 150 mg/day [13]. In other studies of invasive candidiasis, other antifungal agents have not demonstrated a higher success rate or improvement in survival relative to that found in the current study for caspofungin at the standard maintenance dosage of 50-mg/day [14–17]. Overall, these results support the recommended standard dosing regimen for caspofungin.

Although this study was not specifically designed to address this issue, the "paradoxical" effect of reduced activity with higher doses of caspofungin was not observed for the 150-mg dose in the current study. This paradoxical growth effect (also known as the "Eagle effect") among several different *Candida* species has been described for the echinocandins (including caspofungin) in several preclinical in vitro studies [18–20]. The lack of a sufficient clinical correlation of this preclinical finding on the basis of the results of the current study calls into question the clinical relevance of this phenomenon for doses up to 150 mg/day. However, the current study cannot rule out the potential for a paradoxical effect to be observed in patients receiving caspofungin dosages >150 mg/day.

From a clinical perspective, this study provides important safety and efficacy data to guide prescribers who are considering a higher dose of caspofungin as part of a patient's treatment plan. Both the 50-mg and 150-mg dosing regimens for caspofungin treatment were effective and well tolerated in adult patients with invasive candidiasis. The results demonstrate a large safety margin for caspofungin, thereby allowing physicians the option of using higher-dose therapy if a demonstrated need arises.

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