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ARTICLE

Efficacy and safety of caspofungin therapy in elderly patients with proven or suspected invasive fungal infections

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Abstract Invasive fungal infections (IFIs) are serious complications in elderly adults. Caspofungin may provide a useful therapeutic option for elderly patients with or at high risk for IFIs. We retrospectively compared efficacy and safety outcomes in elderly (≥65 years of age) and non-elderly patients in three clinical trials of caspofungin: a double-blind, randomized trial versus amphotericin B for documented invasive candidiasis (IC); an open-label, non-comparative study of definite or probable invasive aspergillosis (IA); and a double-blind, randomized trial versus liposomal amphotericin B as empirical therapy (ET) in febrile neutropenic patients. A total of 159 elderly patients with a median age of 71 years (range, 65–84) received caspofungin in these studies. The median duration of caspofungin therapy was 12 days for IC and ET, and 28 days for IA. Point estimates for the favorable response rates to caspofungin were numerically higher in elderly versus non-elderly patients with IC (83% vs. 68%) or IA (64% vs. 44%) and were similar in patients receiving ET (36% vs. 34%). Adverse events related to caspofungin occurred in generally similar proportions of elderly versus non-elderly patients with IC (clinical, 33% vs. 27%; laboratory, 17% vs. 29%), with IA (clinical, 7% vs. 13%; laboratory, 13% vs. 14%), or receiving ET (clinical, 47% vs. 47%; laboratory, 24% vs. 22%). Nephrotoxicity and infusion-related toxicity developed in comparable proportions of elderly and non-elderly caspofungin recipients in all three studies. In this post-hoc analysis, caspofungin appeared to be as efficacious and well tolerated in elderly patients as in non-elderly patients.

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Introduction

Invasive fungal infections, such as candidiasis and aspergillosis, are emerging problems in elderly patients. Candidiasis is the most common opportunistic fungal infection in older adults [1]. Risk factors include frequent and prolonged hospital stays (especially in medical-surgical intensive care units [2]), renal failure, total parenteral nutrition, central Venous catheters, broad-spectrum antibiotics, and prior surgical procedures [3]. Increasing age is associated with a higher mortality rate among patients with candidemia [4]. More elderly patients are at risk for aspergillus infection because they are severely immunocompromised due to organ transplantation, cancer therapy, or immunosuppressant medications for autoimmune diseases [5]. Aspergillus infections are associated with high mortality rates regardless of age [6].

Treatment of invasive fungal infections in elderly patients must account for age-related physiological changes, a higher prevalence of chronic diseases, and the use of multiple medications, potentially resulting in lower

response rates and/or more adverse drug effects than in younger patients [7, 8]. Invasive fungal infections have traditionally been treated with amphotericin B deoxycholate and more recently with lipid formulations of amphotericin B and azole drugs. Nephrotoxicity associated with amphotericin B is of particular concern in the elderly because of age-related decreases in renal function [5], while therapy with certain azoles may be complicated by potentially dangerous drug interactions [9, 10].

Caspofungin is an echinocandin antifungal agent with activity against *Candida* and *Aspergillus* species. In a single-dose study involving healthy subjects, no meaningful alteration in caspofungin pharmacokinetics based on age (<65 or ≥65 years) was observed [11]. Caspofungin has been shown to be effective as primary treatment in patients with invasive candidiasis [12], as salvage therapy in patients with invasive aspergillosis [13], and as empirical antifungal therapy in patients with persistent fever and neutropenia despite treatment with antibacterial agents [14]. In each of these studies, caspofungin was well tolerated overall, and few serious drug-related adverse events or discontinuations due to drug-related adverse events were reported. To further assess the efficacy and safety of caspofungin in elderly patients, we conducted a post-hoc analysis comparing elderly patients to younger patients in terms of the primary efficacy and safety outcomes using data from the above-cited therapeutic trials of caspofungin for invasive candidiasis [12], invasive aspergillosis [13], and persistent fever and neutropenia [14].

Methods

Study design

This post-hoc analysis was based on data from three completed clinical studies of caspofungin as targeted or empirical therapy for invasive fungal infections: the Invasive Candidiasis Study (protocol 014) [12], the Invasive Aspergillosis Study (protocol 019) [13], and the Empirical Therapy Study (protocol 026) [14]. These trials all included elderly patients, used the same caspofungin dosage (a single 70-mg loading dose on day 1, followed by a maintenance dose of 50 mg/day), and collected comparable safety data. Details of the individual study designs, including the primary efficacy outcome variable for each study, are shown in Table 1.

In all three trials, the following safety outcomes were assessed: drug-related clinical and laboratory adverse events, all-cause mortality, nephrotoxicity, and infusion-related toxicity. Adverse events judged by the investigator to be possibly, probably, or definitely caused by the study drug were considered to be drug-related. Nephrotoxicity was defined as a doubling of baseline serum creatinine level or an increase of ≥1 mg/dl in patients whose baseline serum creatinine level was already above the upper limit of normal; patients with an estimated baseline creatinine clearance ≤30 ml/min were not considered to be evaluable for nephrotoxicity. Infusion-related toxicity was assessed daily based on the presence or absence of systemic infusion-related reactions (e.g., fever, rigors, nausea, headache, hypotension, tachycardia, or anaphylaxis) that occurred during or within 1 h following completion of infusion of the study drug. In addition, local reactions at the infusion site were assessed daily in the invasive candidiasis and invasive aspergillosis studies, and an overall assessment of local tolerability (i.e., well tolerated, moderately well tolerated, or poorly tolerated) was made upon completion of IV study therapy.

Statistical analysis

The primary efficacy analyses for the three studies included all patients who received at least one dose of study therapy and had a confirmed diagnosis of invasive candidiasis, invasive aspergillosis, or persistent fever with neutropenia (depending on the clinical trial). In the invasive candidiasis study, the outcome was considered unfavorable if the study drug was withdrawn before documented improvement occurred, or if toxic effects required a change in antifungal therapy. Summary statistics for the safety parameters included all treated patients. For the current post-hoc analysis, patients were divided into two age groups: those ≥65 years of age (hereafter referred to as "elderly") and those <65 years of age (hereafter referred to as "non-elderly").

Within each treatment group and trial, the differences (and corresponding 95% exact confidence intervals) between the two age groups were calculated using StatXact [15] with respect to the percentage of patients with favorable efficacy responses to study therapy, drug-related adverse events (all, serious, or leading to discontinuation of study therapy), all-cause mortality, nephrotoxicity, and infusion-related toxicity. Because this exploratory subgroup analysis was not specified in the original protocols, formal comparisons between age or treatment groups were not performed.

Results

Patient accounting and baseline characteristics

Of the 768 caspofungin recipients in the three clinical trials, 159 (21%) were elderly: 43 of 114 patients (38%) with invasive candidiasis, 15 of 90 patients (17%) with invasive

Table 1 Study details*

Indication	Study design	Study population	Treatment groups	Primary efficacy outcome
Invasive candidiasis (IC); protocol 014 [12]	Randomized, double-blind, multicenter study; stratified by APACHE II score (≤20 vs. >20) and neutropenic status (ANC <500/μl vs. ≥500/μl)	Patients ≥18 years old with clinically and microbiologically documented IC; excluded if hemoglobin <8 g/dl, platelets <5,000/μl (if neutropenic) or <50,000/μl (if non-neutropenic), bilirubin or alkaline phosphatase >3× ULN, or AST or ALT >5× ULN	Caspofungin 50 mg daily (after a 70-mg loading dose on day 1) or amphotericin B deoxycholate 0.6 to 0.7 mg/kg daily, for 14 days after last positive *Candida* culture; could switch to oral fluconazole after 10 days	Favorable response defined as complete resolution of symptoms and signs attributable to *Candida* infection plus eradication of *Candida* from follow-up cultures
Invasive aspergillosis (IA); protocol 019 [13]	Open-label, noncomparative, multicenter study	Patients ≥18 years old with definite or probable IA refractory to or intolerant of amphotericin or itraconazole; excluded if hemoglobin <8 g/dl, platelets <25,000/μl, bilirubin or alkaline phosphatase >3× ULN, AST or ALT >5× ULN, or creatinine ≥2.5 mg/dl	Caspofungin 50 mg daily (after a 70-mg loading dose on day 1); duration based on immune status, site and extent of IA, and rapidity of response	Favorable clinical response defined as improvement in attributable symptoms, signs, and radiographic or bronchoscopic findings (either as probable or complete response)
Empirical therapy (ET); protocol 026 [14]	Randomized, double-blind, multicenter study; stratified by risk of fungal infection (high vs. low) and use of systemic antifungal prophylaxis (yes vs. no)	Patients ≥16 years old with persistent fever (>38.0°C) and neutropenia (ANC <500/μl) after ≥96 h of parenteral systemic antibacterial therapy; excluded if platelets <5,000/μl, bilirubin or alkaline phosphatase >3× ULN, or AST or ALT >5× ULN	Caspofungin 50 mg daily (after a 70-mg loading dose on day 1) or liposomal amphotericin B 3 mg/kg daily; for ≥14 days in patients with baseline or breakthrough infection and for up to 72 h after ANC ≥500/mm^3 in all others	Favorable overall response based on five criteria: successful treatment of any baseline fungal infection, absence of breakthrough fungal infection during therapy or within 7 days after end of therapy, survival for 7 days after end of therapy, no early discontinuation due to drug-related toxicity or lack of efficacy, and resolution of fever (<38° C for ≥48 h) during neutropenia

ANC, absolute neutrophil count; UNL, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase
*Key information is summarized here; further details are available in the primary study reports cited for each study

aspergillosis, and 101 of 564 patients (18%) receiving empirical therapy (Table 2). Across the three studies, the median age of the elderly patients ranged from 69 to 72 years, and the median age of the non-elderly patients ranged from 44 to 48 years. In the Invasive Candidiasis Study, the distributions of APACHE II scores, neutropenia status, and site of invasive *Candida* infection (blood vs. non-blood) were similar between elderly and non-elderly patients. In the Invasive Aspergillosis Study, most elderly patients (73%) had a hematologic malignancy, whereas the underlying diseases in the non-elderly group were much more heterogeneous. In addition, fewer elderly than non-elderly patients were neutropenic (13% vs. 27%). In the Empirical Therapy Study, leukemia was the most common primary condition in both age groups. Fewer elderly than non-elderly patients were in the high-risk stratum (14% vs. 29%), but

Table 2 Patient characteristics

	Caspofungin		Amphotericin B[a]		Liposomal amphotericin B[b]	
	Elderly (N=159)	Non-elderly (N=609)	Elderly (N=35)	Non-elderly (N=90)	Elderly (N=87)	Non-elderly (N=460)
Age (years)						
Median	69.0	47.0	72.0	47.0	69.0	46.0
Range	65 to 84	15 to 64	65 to 81	18 to 64	65 to 83	16 to 64
Gender, n (%)						
Male	83 (52.2)	364 (59.8)	24 (68.6)	50 (55.6)	55 (63.2)	242 (52.6)
Female	76 (47.8)	245 (40.2)	11 (31.4)	40 (44.4)	32 (36.8)	218 (47.4)
Race, n (%)						
Caucasian	146 (91.8)	530 (87.0)	29 (82.9)	61 (67.8)	83 (95.4)	401 (87.2)
Black	5 (3.1)	26 (4.3)	0 (0.0)	7 (7.8)	2 (2.3)	17 (3.7)
Asian	0 (0.0)	14 (2.3)	0 (0.0)	2 (2.2)	0 (0.0)	13 (2.8)
Hispanic	7 (4.4)	26 (4.3)	6 (17.1)	13 (14.4)	1 (1.1)	13 (2.8)
Other	1 (0.6)	13 (2.1)	0 (0.0)	7 (7.8)	1 (1.1)	16 (3.5)
Site of infection, n (%)						
Candidemia	35 (22.0)	59 (9.7)	28 (80.0)	68 (75.6)	–	–
Non-blood candidiasis	8 (5.0)	12 (2.0)	7 (20.0)	22 (24.4)	–	–
Pulmonary aspergillosis	12 (7.5)	64 (10.5)	–	–	–	–
Other aspergillus infection	3 (1.9)	11 (1.8)	–	–	–	–
Suspected fungal infection	101 (63.5)	463 (76.0)	–	–	87 (100)	460 (100)
Neutropenia status, n (%)						
ANC<500/ul	108 (67.9)	492 (80.8)	1 (2.9)	11 (12.2)	87 (100)	460 (100)

[a] In patients with invasive candidiasis
[b] In patients receiving empirical antifungal therapy

relatively similar proportions of elderly and non-elderly patients had received antifungal prophylaxis (49% vs. 58%). The median duration of caspofungin therapy (Table 3) was slightly longer in elderly versus non-elderly patients with invasive aspergillosis (28 vs. 22 days), but was similar in elderly and non-elderly patients with invasive candidiasis (12 vs. 11 days) or receiving empirical therapy (12 vs. 10 days). In the two controlled studies, the median duration of the comparator therapy was also similar in elderly and non-elderly patients (10 vs. 10 days for conventional amphotericin B in the Invasive Candidiasis Study; 9 vs. 10 days for liposomal amphotericin B in the Empirical Therapy Study).

Table 3 Duration of intravenous study therapy (days)

	Caspofungin group		Control group*		Total	
	Elderly	Non-elderly	Elderly	Non-elderly	Elderly	Non-elderly
Invasive candidiasis	(N=43)	(N=71)	(N=35)	(N=90)	(N=78)	(N=161)
Mean	12.1	11.6	9.4	12.1	10.9	11.9
Median	12.0	11.0	10.0	10.0	11.0	10.0
Range	1 to 23	2 to 28	1 to 19	1 to 28	1 to 23	1 to 28
Invasive aspergillosis	(N=15)	(N=75)	(NA)	(NA)	(N=15)	(N=75)
Mean	31.2	32.8	–	–	31.2	32.8
Median	28.0	22.0	–	–	28.0	22.0
Range	5 to 77	1 to 162	–	–	5 to 77	1 to 162
Empirical therapy	(N=101)	(N=463)	(N=87)	(N=460)	(N=188)	(N=923)
Mean	13.0	13.0	11.3	12.8	12.2	12.9
Median	12.0	10.0	9.0	10.0	10.0	10.0
Range	2 to 38	1 to 90	1 to 61	1 to 90	1 to 61	1 to 90

*Amphotericin B deoxycholate in the invasive candidiasis study; liposomal amphotericin B in the empirical therapy study
NA = not applicable

Table 4 Efficacy outcomes by study

	Elderly	Non-elderly	Difference[b]	Elderly	Non-elderly	Difference[b]
	m/n[a] (%) (95% CI)	m/n[a] (%) (95% CI)	% (95% CI)	m/n[a] (%) (95% CI)	m/n[a] (%) (95% CI)	% (95% CI)
Invasive candidiasis	Caspofungin			Amphotericin B		
Favorable response at end of IV study therapy	33/40 (82.5) (67.2, 92.7)	47/69 (68.1) (55.8, 78.8)	14.4 (−4.9, 34.6)	14/33 (42.4) (25.5, 60.8)	57/82 (69.5) (58.4, 79.2)	−27.1 (−48.6, −6.8)
Invasive aspergillosis	Caspofungin					
Favorable response at end of IV study therapy	9/14 (64.3) (35.1, 87.2)	31/70 (44.3) (32.4, 56.7)	20.0 (−9.7, 48.3)	NA	NA	NA
Empirical therapy	Caspofungin			Liposomal amphotericin B		
Overall favorable response	36/100 (36.0) (26.6, 46.2)	154/456 (33.8) (29.4, 38.3)	2.2 (−8.3, 14.1)	24/85 (28.2) (19.0, 39.0)	157/454 (34.6) (30.2, 39.2)	−6.3 (−18.2, 5.2)
Successful treatment of baseline fungal infection[c]	4/8 (50.0) (15.7, 84.3)	10/19 (52.6) (28.9, 75.6)	−2.6 (−53.1, 38.5)	1/4 (25.0) (0.6, 80.6)	6/23 (26.1) (10.2, 48.4)	−1.1 (−55.0, 52.6)
No breakthrough invasive fungal infection	95/100 (95.0) (88.7, 98.4)	432/456 (94.7) (92.3, 96.6)	0.3 (−7.2, 9.0)	84/85 (98.8) (93.6, 100.0)	432/454 (95.2) (92.8, 96.9)	3.7 (−3.1, 9.1)
Survival to 7 days post therapy	90/100 (90.0) (82.4, 95.1)	425/456 (93.2) (90.5, 95.3)	−3.2 (−13.0, 3.3)	66/85 (77.6) (67.3, 86.0)	415/454 (91.4) (88.4, 93.8)	−13.8 (−25.8, −4.6)
No treatment-related discontinuation	87/100 (87.0) (78.8, 92.9)	412/456 (90.4) (87.3, 92.9)	−3.4 (−13.7, 3.9)	67/85 (78.8) (68.6, 86.9)	394/454 (86.8) (83.3, 89.8)	−8.0 (−20.1, 1.3)
Resolution of fever for 48 h during neutropenia	47/100 (47.0) (36.9, 57.2)	182/456 (39.9) (35.4, 44.6)	7.1 (−3.8, 18.9)	34/85 (40.0) (29.5, 51.2)	189/454 (41.6) (37.1, 46.3)	−1.6 (−13.5, 10.0)

[a] m/n = Number of patients with the corresponding endpoint/number of patients in the analysis
[b] Difference = response rate in elderly patients minus response rate in non-elderly patients
[c] Only patients with a baseline infection are included in this analysis
NA = not applicable

Efficacy outcomes

A favorable response to caspofungin was observed in more elderly than non-elderly patients with invasive candidiasis (83% vs. 68%) or invasive aspergillosis (64% vs. 44%). Conversely, fewer elderly than non-elderly patients with invasive candidiasis had a favorable response to amphotericin B (42% vs. 70%); this difference amphotericin B recipients largely reflects the higher discontinuation rate in the elderly group (see below). In the Empirical Therapy Study, an overall favorable response occurred in similar proportions of elderly and non-elderly patients in both treatment groups (Table 4). Both treatment groups also had similar proportions of elderly and non-elderly patients with a favorable response on the individual outcome components, except that survival to 7 days post-therapy was lower in elderly patients versus non-elderly patients receiving liposomal amphotericin B (78% vs. 91%).

Safety outcomes

In all three studies, clinical and laboratory adverse events related to caspofungin occurred in similar proportions of elderly and non-elderly patients (Table 5). Very few patients in either age group had caspofungin-related clinical or laboratory adverse events that were serious (0–4%) or led to treatment discontinuation (0–5%). Among patients who received liposomal amphotericin B in the Empirical Therapy Study, elderly and non-elderly patients had comparable rates of drug-related adverse events (Table 5). By contrast, in the Invasive Candidiasis Study, amphotericin-related adverse events leading to treatment discontinuation were more common in elderly versus non-elderly patients (49% vs. 20%). Among caspofungin recipients and liposomal amphotericin B recipients, the types and frequencies of specific drug-related adverse events were generally similar in elderly and non-elderly patients, whereas elderly patients receiving conventional amphotericin B had numerically higher rates of tachycardia, tachypnea, and increased bilirubin compared with non-elderly patients (Table 6).

The all-cause mortality rate was modestly higher in elderly patients versus non-elderly patients in both treatment groups in the Invasive Candidiasis Study and the Empirical Therapy Study, but was slightly lower in elderly versus non-elderly patients in the Invasive Aspergillosis Study (Table 5). Nephrotoxicity and systemic infusion-related events occurred in similar proportions of elderly and

Table 5 Summary of adverse events (AEs) by study

	Caspofungin group			Control group*		
	Elderly n (%)	Non-elderly n (%)	Difference[a] % (95% CI)	Elderly n (%)	Non-elderly n (%)	Difference[a] % (95% CI)
Invasive candidiasis	(N=43)	(N=71)		(N=35)	(N=90)	
Drug-related clinical AEs	14 (32.6)	19 (26.8)	5.8 (−12.7, 26.9)	19 (54.3)	54 (60.0)	−5.7 (−27.8, 13.9)
Serious	0 (0.0)	1 (1.4)	−1.4 (−13.2, 10.6)	5 (14.3)	11 (12.2)	2.1 (−13.3, 24.0)
Leading to therapy discontinuation	0 (0.0)	3 (4.2)	−4.2 (−18.2, 8.3)	9 (25.7)	12 (13.3)	12.4 (−5.1, 34.2)
Drug-related laboratory AEs	7/41 (17.1)	20/69 (29.0)	−11.9 (−32.1, 7.0)	22/35 (62.9)	45/89 (50.6)	12.3 (−7.6, 32.6)
Serious	0/41 (0.0)	0/69 (0.0)	0.0 (−10.4, 11.9)	1/35 (2.9)	1/89 (1.1)	1.7 (−7.6, 21.0)
Leading to therapy discontinuation	0/41 (0.0)	1/69 (1.4)	−1.4 (−13.6, 10.7)	8/35 (22.9)	6/89 (6.7)	16.1 (−0.2, 37.7)
All-cause mortality	18 (41.9)	21 (29.6)	12.3 (−6.7, 33.1)	17 (48.6)	21 (23.3)	25.2 (5.7, 46.3)
Nephrotoxicity[b]	2/34 (5.9)	6/61 (9.8)	−4.0 (−26.0, 14.1)	6/28 (21.4)	20/77 (26.0)	−4.5 (−27.1, 17.3)
Infusion-related toxicity[c]	5 (11.6)	18 (25.4)	−13.7 (−33.6, 4.3)	13 (37.1)	48 (53.3)	−16.2 (−36.1, 3.6)
Invasive aspergillosis	(N=15)	(N=75)		(NA)	(NA)	
Drug-related clinical AEs	1 (6.7)	10 (13.3)	−6.7 (−30.4, 21.5)	–	–	–
Serious	0 (0.0)	1 (1.3)	−1.3 (−12.6, 24.9)	–	–	–
Leading to therapy discontinuation	0 (0.0)	1 (1.3)	−1.3 (−12.6, 24.9)	–	–	–
Drug-related laboratory AEs	2/15 (13.3)	10/74 (13.5)	−0.2 (−29.2, 27.9)	–	–	–
Serious	0/15 (0.0)	1/74 (1.4)	−1.4 (−12.7, 24.7)	–	–	–
Leading to therapy discontinuation	0/15 (0.0)	1/74 (1.4)	−1.4 (−12.7, 24.7)	–	–	–
All-cause mortality	6 (40.0)	38 (50.7)	−10.7 (−38.6, 17.9)	–	–	–
Nephrotoxicity[b]	1/12 (8.3)	10/63 (15.9)	−7.5 (−35.4, 23.8)	–	–	–
Infusion-related toxicity[c]	1 (6.7)	12 (16.0)	−9.3 (−33.7, 18.9)	–	–	–
Empirical therapy	(N=101)	(N=463)		(N=87)	(N=460)	
Drug-related clinical AEs	47 (46.5)	218 (47.1)	−0.5 (−11.6, 10.3)	58 (66.7)	268 (58.3)	8.4 (−3.1, 20.1)
Serious	4 (4.0)	5 (1.1)	2.9 (−1.1, 10.7)	3 (3.4)	13 (2.8)	0.6 (−3.7, 9.5)
Leading to therapy discontinuation	5 (5.0)	20 (4.3)	0.6 (−4.3, 9.3)	6 (6.9)	29 (6.3)	0.6 (−5.4, 10.6)
Drug-related laboratory AEs	24/101 (23.8)	103/463 (22.2)	1.5 (−7.8, 13.0)	28/87 (32.2)	147/460 (32.0)	0.2 (−10.6, 12.9)
Serious	0/101 (0.0)	0/463 (0.0)	0.0 (−1.6, 4.9)	1/87 (1.1)	0/460 (0.0)	1.1 (−1.1, 8.3)
Leading to therapy discontinuation	0/101 (0.0)	3/463 (0.6)	−0.6 (−3.0, 4.3)	5/87 (5.7)	8/460 (1.7)	4.0 (−0.9, 1.3)
All-cause mortality	18 (17.8)	43 (9.3)	8.5 (0.5, 19.2)	21 (24.1)	54 (11.7)	12.4 (2.9, 24.5)
Nephrotoxicity[b]	4/98 (4.1)	10/449 (2.2)	1.9 (−2.5, 10.1)	10/83 (12.0)	50/439 (11.4)	0.7 (−7.1, 12.1)
Infusion-related toxicity[c]	32 (31.7)	166 (35.9)	−4.2 (−15.2, 6.6)	44 (50.6)	238 (51.7)	−1.2 (−13.9, 10.4)

*Amphotericin B deoxycholate in the invasive candidiasis study; liposomal amphotericin B in the empirical therapy study
[a] Difference = elderly patients minus non-elderly patients
[b] Doubling of serum creatinine (or increased by =1 mg/dl if elevated at baseline) in patients with baseline creatinine clearance >30 ml/min
[c] As assessed by the investigator
NA = not applicable

non-elderly patients in all treatment groups in all three studies (Table 5). Infusion-site tolerability was also similar in elderly and non-elderly patients: caspofungin infusion was well-tolerated in over 95% of both age groups; amphotericin B infusion was well tolerated in 100% of elderly patients and 89% of non-elderly patients.

Discussion

Serious fungal infections are becoming more frequent in the elderly due to the increasing use of aggressive chemotherapy and other immunosuppressive medications in this age group, along with increased amounts of time spent in intensive care units. We therefore conducted a post-hoc analysis of the safety and efficacy of caspofungin in elderly patients with invasive candidiasis, invasive aspergillosis, or persistent fever and neutropenia. Assessment of new drugs specifically in elderly populations is informative because older patients may be particularly prone to drug toxicities and drug-drug interactions as a consequence of decreased organ function and multiple concomitant medications. Additionally, efficacy responses may be diminished in the elderly as a result of multiple comorbid conditions and age-related physiologic changes.

Table 6 Most common[a] drug-related[b] adverse events

	Caspofungin				Amphotericin B				Liposomal amphotericin B			
	Elderly (N=159) n (%)		Non-elderly (N=609) n (%)		Elderly (N=35) n (%)		Non-elderly (N=90) n (%)		Elderly (N=87) n (%)		Non-elderly (N=460) n (%)	
Clinical adverse events												
Chills	16	(10.1)	68	(11.2)	8	(22.9)	25	(27.8)	21	(24.1)	114	(24.8)
Fever	12	(7.5)	94	(15.4)	6	(17.1)	23	(25.6)	18	(20.7)	88	(19.1)
Jaundice	3	(1.9)	0	(0.0)	4	(11.4)	0	(0.0)	1	(1.1)	3	(0.7)
Nausea	7	(4.4)	17	(2.8)	0	(0.0)	7	(7.8)	12	(13.8)	50	(10.9)
Renal insufficiency	3	(1.9)	4	(0.7)	4	(11.4)	10	(11.1)	4	(4.6)	6	(1.3)
Tachycardia	2	(1.3)	8	(1.3)	8	(22.9)	5	(5.6)	4	(4.6)	9	(2.0)
Tachypnea	0	(0.0)	2	(0.3)	7	(20.0)	6	(6.7)	5	(5.7)	6	(1.3)
Vomiting	3	(1.9)	23	(3.8)	0	(0.0)	10	(11.1)	7	(8.0)	40	(8.7)
Laboratory adverse events												
ALT increased	10/155	(6.5)	44/603	(7.3)	4/34	(11.8)	6/89	(6.7)	9/86	(10.5)	39/456	(8.6)
AST increased	8/156	(5.1)	34/595	(5.7)	5/34	(14.7)	6/88	(6.8)	7/86	(8.1)	34/455	(7.5)
Alkaline phosphatase increased	8/155	(5.2)	42/601	(7.0)	8/35	(22.9)	11/87	(12.6)	13/85	(15.3)	52/455	(11.4)
Direct bilirubin increased	4/104	(3.8)	9/409	(2.2)	6/28	(21.4)	2/67	(3.0)	4/60	(6.7)	16/327	(4.9)
Total bilirubin increased	6/155	(3.9)	15/604	(2.5)	7/35	(20.0)	4/89	(4.5)	6/86	(7.0)	22/457	(4.8)
BUN increased	4/107	(3.7)	4/341	(1.2)	8/34	(23.5)	11/86	(12.8)	3/44	(6.8)	5/211	(2.4)
Serum creatinine increased	6/157	(3.8)	6/602	(1.0)	8/35	(22.9)	20/89	(22.5)	4/87	(4.6)	26/458	(5.7)
Serum potassium decreased	12/157	(7.6)	42/605	(6.9)	6/35	(17.1)	23/89	(25.8)	8/86	(9.3)	56/458	(12.2)
Hemoglobin decreased	1/156	(0.6)	0/604	(0.0)	4/35	(11.4)	9/89	(10.1)	0/86	(0.0)	2/457	(0.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen
[a] Occurring in at least 10% of one or more treatment groups
[b] Determined by investigator to be possibly, probably or definitely related to study therapy

In our analysis, the efficacy of caspofungin was comparable in elderly and non-elderly patients with documented invasive candidiasis or invasive aspergillosis, or with suspected invasive fungal infections in the context of febrile neutropenia. The adverse-event profile of caspofungin appeared to be generally similar in elderly and non-elderly patients. No meaningful differences were evident between elderly and non-elderly caspofungin recipients in the overall incidence of clinical and laboratory drug-related adverse events or the types and frequencies of the most common specific drug-related adverse events. In addition, nephrotoxicity and infusion-related toxicity were not increased in elderly versus non-elderly caspofungin recipients.

The studies included in this analysis were not designed to compare treatment effects in patient subgroups based on age. There may be relevant differences between elderly and non-elderly subgroups in important baseline characteristics because patients were not stratified by age. The characteristics of study participants may not always reflect those of the general population, potentially limiting the extrapolation of these findings to the elderly population at large. For example, some physicians may choose not to enroll selected elderly patients with candidiasis in trials where the comparator drug is amphotericin B deoxycholate instead of the less nephrotoxic, but narrower-spectrum fluconazole. Firm conclusions about the relative efficacy and safety of antifungal agents in elderly patients should not be drawn from this analysis [16–18]. Nevertheless, our results suggest that caspofungin is efficacious and well tolerated in elderly patients, consistent with its overall profile in adults [12–14]. Caspofungin provides a therapeutic alternative to amphotericin B for many elderly patients with documented or suspected invasive fungal infections.

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