

## Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

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### ABSTRACT

#### BACKGROUND

Patients with persistent fever and neutropenia often receive empirical therapy with conventional or liposomal amphotericin B for the prevention and early treatment of invasive fungal infections. Caspofungin, a member of the new echinocandin class of compounds, may be an effective alternative that is better tolerated than amphotericin B.

#### METHODS

In this randomized, double-blind, multinational trial, we assessed the efficacy and safety of caspofungin as compared with liposomal amphotericin B as empirical antifungal therapy. At study entry, patients were stratified according to risk and according to whether they had previously received antifungal prophylaxis. A successful outcome was defined as the fulfillment of all components of a five-part composite end point.

#### RESULTS

Efficacy was evaluated in 1095 patients (556 receiving caspofungin and 539 receiving liposomal amphotericin B). After adjustment for strata, the overall success rates were 33.9 percent for caspofungin and 33.7 percent for liposomal amphotericin B (95.2 percent confidence interval for the difference, -5.6 to 6.0 percent), fulfilling statistical criteria for the noninferiority of caspofungin. Among patients with baseline fungal infections, a higher proportion of those treated with caspofungin had a successful outcome (51.9 percent vs. 25.9 percent,  $P=0.04$ ). The proportion of patients who survived at least seven days after therapy was greater in the caspofungin group (92.6 percent vs. 89.2 percent,  $P=0.05$ ). Premature study discontinuation occurred less often in the caspofungin group than in the amphotericin B group (10.3 percent vs. 14.5 percent,  $P=0.03$ ). The rates of breakthrough fungal infections and resolution of fever during neutropenia were similar in the two groups. Fewer patients who received caspofungin sustained a nephrotoxic effect (2.6 percent vs. 11.5 percent,  $P<0.001$ ), an infusion-related event (35.1 percent vs. 51.6 percent,  $P<0.001$ ), or a drug-related adverse event or discontinued therapy because of drug-related adverse events.

#### CONCLUSIONS

Caspofungin is as effective as and generally better tolerated than liposomal amphotericin B when given as empirical antifungal therapy in patients with persistent fever and neutropenia.

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N Engl J Med 2004;351:1391-402.

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**I**NVASIVE FUNGAL INFECTIONS ARE IMPORTANT causes of illness and death in patients with neutropenia who receive chemotherapy for cancer or who undergo hematopoietic stem-cell transplantation.<sup>1-3</sup> Persistent fever in patients with neutropenia who are receiving broad-spectrum antibiotics may be the only clinical indication of an invasive fungal infection.

Amphotericin B and its lipid formulations, as well as triazoles (fluconazole, itraconazole, and voriconazole), have been studied as empirical antifungal agents in patients with persistent fever and neutropenia.<sup>4-11</sup> However, these agents may be associated with toxicity and adverse drug interactions and have a limited spectrum of activity, erratic bioavailability, unpredictable pharmacokinetics, and limited efficacy. There is therefore a critical need for new classes of antifungal agents for use as empirical therapy in patients with persistent fever and neutropenia.

Echinocandins are a relatively new class of antifungal agents that noncompetitively inhibit the synthesis of fungal cell-wall 1,3- $\beta$ -D-glucan. Caspofungin has activity against candida species and aspergillus species<sup>12-16</sup> and has been approved for the primary treatment of esophageal candidiasis, candidemia, and other candida infections (intraabdominal abscesses, peritonitis, and pleural-space infections) and for the treatment of invasive aspergillosis that is refractory to or intolerant of other antifungal therapy.<sup>17-21</sup> We therefore investigated the efficacy and safety of caspofungin as compared with those of liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia.

## METHODS

### STUDY DESIGN

This was a prospective, double-blind study conducted from January 2000 through August 2002 at 116 sites in 26 countries. Written informed consent was obtained from all the patients, and all the institutional review boards approved of the protocol and consent form. No modifications to the protocol procedures were made during the course of the study.

### RANDOMIZATION

After persistent fever and neutropenia had been documented, patients who fulfilled all the other enrollment criteria were eligible for randomization.

Randomization in a 1:1 ratio was performed at each site with the use of a blocking factor of four. Before randomization, patients were stratified according to two variables: risk (high or low) and use of systemic antifungal prophylaxis (yes or no). High-risk patients were those who had undergone allogeneic stem-cell transplantation or who had relapsed acute leukemia; low-risk patients were all others. Separate random-assignment schedules were used for high-risk and low-risk patients; for patients who had used systemic antifungal prophylaxis and those who had not, the lowest and highest random-assignment numbers available, respectively, on the appropriate assignment schedules were used.

### DATA AND SAFETY MONITORING BOARD AND ADJUDICATION COMMITTEE

When the study began, an independent data and safety monitoring board and adjudication committee were appointed. The data and safety monitoring board, composed of clinicians and a statistician not connected with the study, monitored all the blinded safety data and, at a prespecified time, reviewed the unblinded efficacy and safety data to determine whether the study should continue. No changes to the study were made on the basis of this review.

The adjudication committee, composed of two of the authors and one specialist in infectious diseases, all of whom had extensive experience in the treatment of fungal infections, reviewed the blinded data and classified all suspected fungal infections (as proven, probable, or possible infections or as not fungal infections) on the basis of prespecified consensus criteria defined by the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.<sup>22</sup> The adjudication committee members also determined the causal pathogen, time of onset of infection, and response of baseline infections to study treatment, according to a prespecified protocol. Baseline infections were those present on or before day 2 of the study, and breakthrough infections those with an onset on day 3 or later. The assessments of the adjudication committee were final, and only fungal infections that the committee judged to be probable or proven were considered documented infections for the purpose of study analysis.

### BLINDING

Blinding was rigorously conducted by means of a double-blind, double-dummy procedure. Opaque

covers were used to conceal the infusion bags and catheters used for infusions of liposomal amphotericin B and the corresponding placebo. The placebo infusions were color-matched to the corresponding active-drug infusions; for the placebo corresponding to liposomal amphotericin B, a multivitamin solution was added to 5 percent dextrose to create a yellow solution, and for the placebo corresponding to caspofungin, normal saline was used.

#### PATIENTS

Male and female patients 16 years of age or older were eligible to participate if they had received chemotherapy for cancer or had undergone hematopoietic stem-cell transplantation and if they had had an absolute neutrophil count below 500 per cubic millimeter for at least 96 hours, had fever (a temperature above 38.0°C), and had received parenteral antibacterial therapy for at least 96 hours. Patients were not eligible if they had an inadequately managed bacterial infection, documented invasive fungal infection, or a Karnofsky score below 30 (on a scale from 0 to 100, where lower scores indicate worse function) at the time of enrollment. Other exclusion criteria were a history of serious allergy to the study drugs, a bilirubin or alkaline phosphatase level more than three times the upper limit of normal, an aspartate or alanine aminotransferase level more than five times the upper limit of normal, a platelet count below 5000 per cubic millimeter, and a requirement for rifampin, cyclosporine, or concomitant systemic antifungal therapy.

#### STUDY THERAPY

Patients were assigned to receive either intravenous caspofungin (70 mg on day 1 and 50 mg once daily thereafter) plus placebo corresponding to liposomal amphotericin B or liposomal amphotericin B (3.0 mg per kilogram of body weight daily) plus placebo corresponding to caspofungin. Premedication was not allowed on day 1, but if an infusion-related reaction occurred, its administration was subsequently allowed. If the study therapy was well tolerated but fever persisted for five or more days and the patient's clinical condition deteriorated, the dosage could be increased (to 70 mg once daily in the case of caspofungin and to 5.0 mg per kilogram per day in the case of liposomal amphotericin B). For patients who did not have evidence of baseline or breakthrough fungal infection, study therapy was administered until the absolute neutrophil count

was at least 500 per cubic millimeter and for up to 72 hours thereafter. The on-site investigator determined the duration of therapy for patients with baseline or breakthrough fungal infections; however, it was recommended that treatment be given for at least 14 days and for at least 7 days after neutropenia and symptoms resolved.

#### ANALYSIS

The population in whom the primary efficacy analysis was conducted was a modified intention-to-treat population, comprising patients with persistent fever and neutropenia who had been randomly assigned to a study group and who had received at least one complete dose of study medication. Safety and tolerability were assessed in all patients who received at least one dose of active study drug.

#### *Efficacy Assessments*

The primary efficacy end point was a favorable overall response, as determined by a five-component end point that has been used in previous studies of empirical antifungal therapy.<sup>4,5,7,8</sup> Treatment was considered successful if all five of the following criteria were met: successful treatment of any baseline fungal infection, absence of any breakthrough fungal infection during therapy or within seven days after the completion of therapy, survival for seven days after the completion of therapy, no premature discontinuation of study therapy because of drug-related toxicity or lack of efficacy, and resolution of fever (defined as a temperature below 38°C for at least 48 hours) during neutropenia. Secondary efficacy assessments consisted of assessments of each component of the primary end point. Survival times were also assessed for the modified intention-to-treat population.

#### *Safety Assessments*

Investigators monitored patients for clinical adverse events daily during the administration of the study therapy and for 14 days thereafter and assessed whether any adverse event was related to the study therapy. Infusion-related events (systemic symptoms during and one hour after infusion) were prospectively defined, evaluated daily, and reported as adverse events. Laboratory studies were performed at the time of enrollment, twice weekly during therapy, at the end of therapy, and two weeks after the end of therapy.

**ROLE OF SPONSOR**

This study was designed by three of the authors (Drs. Walsh and dePauw, in collaboration with Dr. Sable). It was modeled after a previous double-blind trial, the National Institute of Allergy and Infectious Diseases Mycoses Study Group study 32.<sup>5</sup> Two of the authors were involved at all levels in the design, implementation, and analysis phases of the study. Data were collected and analyzed initially by the sponsor. All data in the study were source-documented. All the authors had full access to the primary data and to their analysis. There was full independence in decisions concerning the reporting of results and the content of the manuscript, with no interference from the sponsor.

**STATISTICAL ANALYSIS**

All the primary and secondary analyses presented here, including analyses of the components of the primary end point, were prespecified; no selectivity was used. The primary analysis was designed to show whether the outcome in the caspofungin group was noninferior to that in the liposomal amphotericin B group. According to the prespecified definition, noninferiority with respect to the primary efficacy end point would be demonstrated if the two-sided 95.2 percent confidence interval (calculated with use of the adjusted alpha value of 0.048, on the basis of the interim analysis conducted by the data safety and monitoring board) for the difference in response rates between the treatment groups (the rate with caspofungin minus the rate with liposomal amphotericin B) included 0 and the lower limit was not less than -10 percent (i.e., 10 percentage points in favor of liposomal amphotericin B). An adjustment for stratification was used.

For the overall and individual end points, the observed proportion of patients with a favorable outcome was determined and 95 percent confidence intervals were calculated with use of the normal approximation to the binomial distribution. The analysis plan designated the modified intention-to-treat population as the population for which the primary end point was determined. For the primary end point, the estimated proportion of patients with a favorable overall outcome in each group and its 95 percent confidence interval and the difference in response rates and its 95.2 percent confidence interval were calculated with use of the Cochran-Mantel-Haenszel adjustment for stratification.<sup>23</sup>

Assuming a 50 percent success rate in the liposomal amphotericin B group and a significance level of 4.8 percent, a sample of 530 patients per treatment group in the modified intention-to-treat analysis was chosen to demonstrate noninferiority with a power of 90 percent.

In the analysis of the survival end point in the modified intention-to-treat population, patients who were lost to follow-up within seven days after the completion of therapy were considered to have had treatment failure. Kaplan-Meier estimates of survival time were determined. Differences in survival times between the two treatment groups were assessed with a log-rank test at the 5 percent significance level.

The main safety analysis evaluated the proportion of patients with a baseline creatinine clearance above 30 ml per minute who had nephrotoxicity (a doubling of the serum creatinine level or, if the value was elevated at the time of enrollment, an increase of at least 1 mg per deciliter [88  $\mu$ mol per liter]). In the analysis of nephrotoxicity, noninferiority was demonstrated if the lower limit of the 95 percent confidence interval for the difference in proportions between treatment groups (caspofungin minus liposomal amphotericin B) was 0 or less (where negative values favored caspofungin) and the upper limit was not greater than 5 percent. Infusion-related events, any drug-related adverse events, and drug-related adverse events leading to discontinuation were analyzed by testing the difference in proportions between groups. The most common specific drug-related adverse events were analyzed with the use of 95 percent confidence intervals for the difference in proportions between the treatment groups. All P values were two-sided and were not adjusted for multiple comparisons. P values  $\leq 0.05$  were considered to indicate statistical significance.

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**RESULTS**


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**PATIENTS**

Of 1123 patients who underwent randomization, 1111 were treated and 1095 were included in the modified intention-to-treat population. Baseline demographic characteristics were balanced between the two treatment groups (Table 1). An underlying hematologic cancer was present in 94.2 percent of the patients, predominantly acute myelogenous leukemia. The duration of therapy was similar in

**Table 1. Demographic Characteristics of the Patients in the Modified Intention-to-Treat Population.\***

Characteristic	Caspofungin (N=556)	Liposomal Amphotericin B (N=539)
Female sex — no. (%)	238 (42.8)	247 (45.8)
Age — yr		
Median	51	49
Range	17–83	16–83
Age group — no. (%)		
≤17 yr	3 (0.5)	8 (1.5)
18–40 yr	158 (28.4)	160 (29.7)
41–65 yr	307 (55.2)	297 (55.1)
>65 yr	88 (15.8)	74 (13.7)
Race — no. (%)†		
White	502 (90.3)	476 (88.3)
Black	21 (3.8)	19 (3.5)
Other	33 (5.9)	44 (8.2)
High-risk group — no. (%)	146 (26.3)	122 (22.6)
Allogeneic hematopoietic stem-cell transplantation‡	36 (6.5)	39 (7.2)
Relapse of acute leukemia	110 (19.8)	83 (15.4)
Prior antifungal prophylaxis — no. (%)§	313 (56.3)	304 (56.4)
Primary diagnosis — no. (%)		
Acute myelogenous leukemia	364 (65.5)	339 (62.9)
Acute lymphocytic leukemia	57 (10.3)	50 (9.3)
Non-Hodgkin's lymphoma	58 (10.4)	62 (11.5)
Other¶	77 (13.8)	88 (16.3)
Neutrophil count <100 per mm <sup>3</sup> — no. (%)	400 (71.9)	406 (75.3)

\* The 1095 patients in the modified intention-to-treat population, in which the primary efficacy analysis was conducted, received at least one complete dose of study therapy (i.e., active drug plus placebo) and had persistent fever and neutropenia. Among the 1123 patients who underwent randomization, 12 did not receive any study drug, 15 did not have documented fever or neutropenia at study entry, and 1 did not receive a full dose of study drug. In all, 17 patients were excluded from the caspofungin group (9 because they did not receive study drug), and 11 were excluded from the liposomal amphotericin B group (3 because they did not receive study drug).

† Race was determined by the individual site investigator.

‡ Some of these patients had received chemotherapy for relapse of acute leukemia.

§ Antifungal prophylaxis before enrollment was used at the discretion of the investigator. Fluconazole was the most commonly used agent.

¶ This category included chronic myelogenous leukemia, multiple myeloma, Hodgkin's lymphoma, solid tumors, and the myelodysplastic syndrome.

the two treatment groups: the mean duration was 13.0 days (median, 11 [range, 1 to 90]) in the caspofungin group and 12.5 days (median, 10 [range, 1 to 90]) in the liposomal amphotericin B group.

#### OVERALL RESPONSE

In the analysis of the primary end point, adjusted for strata, 33.9 percent of patients who received caspofungin and 33.7 percent of those who received liposomal amphotericin B had a favorable overall re-

sponse (95.2 percent confidence interval for the difference between caspofungin and liposomal amphotericin B, -5.6 to 6.0 percent) (Table 2); thus, caspofungin fulfilled the statistical criteria for non-inferiority to liposomal amphotericin B. Among high-risk patients in both treatment groups, observed overall response rates were somewhat higher than the rates in low-risk patients. Prior antifungal prophylaxis did not significantly affect overall response rates.

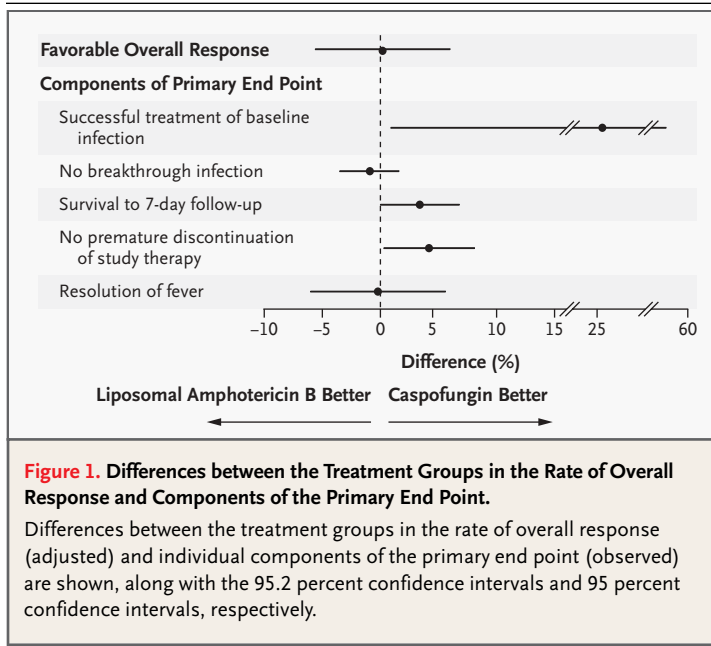
**Table 2. Outcomes of Empirical Antifungal Therapy.\***

End Point	Caspofungin (N=556)	Liposomal Amphotericin B (N=539)	Difference (CI)† percentage points	P Value
<b>Overall favorable response</b>				
Adjusted for strata — no. of patients (%)	190 (33.9)	181 (33.7)	0.2 (–5.6 to 6.0)	
Not adjusted for strata — no. of patients (%)	190 (34.2)	181 (33.6)	—‡	
Observed, according to risk category — no. of patients/total no. (%)				
High risk	63/146 (43.2)	46/122 (37.7)	5.4 (–6.3 to 17.2)	
Low risk	127/410 (31.0)	135/417 (32.4)	–1.4 (–7.7 to 4.9)	
Antifungal prophylaxis				
Antifungal prophylaxis	105/313 (33.5)	100/304 (32.9)		
No antifungal prophylaxis	85/243 (35.0)	81/235 (34.5)		
<b>Observed components of primary end point</b>				
Successful treatment of baseline fungal infection — no. of patients/ no. with infection	14/27 (51.9)	7/27 (25.9)	25.9 (0.9 to 51.0)	0.04
Absence of breakthrough fungal infection — no. of patients/total no.	527 (94.8)	515 (95.5)	–0.8 (–3.3 to 1.8)	0.56
Survival for ≥7 days after completion of study therapy — no. of patients/ total no.§	515 (92.6)	481 (89.2)	3.4 (0.0 to 6.8)	0.05
Resolution of fever in setting of neutropenia — no. of patients/total no.	229 (41.2)	223 (41.4)	–0.2 (–6.0 to 5.6)	0.95
Study therapy discontinued prematurely because of toxicity or lack of efficacy — no. of patients/total no.				
No	499 (89.7)	461 (85.5)	4.2 (0.3 to 8.1)	0.03
Yes				
Lack of efficacy¶	30 (5.4)	34 (6.3)	–0.9 (–3.7 to 1.9)	
Drug toxicity	27 (4.9)	44 (8.2)	–3.3 (–6.2 to –0.4)	
<b>Fungal infections  </b>				
Baseline — no. of patients with successful outcome/ no. of patients with infection (%)**	14/27 (51.9)	7/27 (25.9)		
Aspergillus (all) ††				
Disseminated aspergillosis	—	0/2		
Pneumonia	3/9 (33.3) ¶¶	0/7		
Sinusitis	2/3 (66.7)	0/2		
Paronychia	—	1/1 (100)		
Candida (all)				
Chronic disseminated candidiasis	1/2 (50.0)	—		
Disseminated fungal infection	0/2	0/1		
Fungemia	7/8 (87.5)	5/9 (55.6)		
Empyema	—	0/1		
Pneumonia	—	0/1		
<i>Dipodascus capitatus</i> †††	0/1	—		
Zygomycetes †††	0/1	—		
Fusarium species §§§	—	1/2 (50.0)		
Mold, not further identified ¶¶¶	1/1 (100)	0/1		
Breakthrough — no. of patients with infection**				
Total	29	24		
Aspergillus (all)	10	9		
Disseminated aspergillosis	3	1		

Table 2. (Continued.)

End Point	Caspofungin (N=556)	Liposomal Amphotericin B (N=539)	Difference (CI)† percentage points	P Value
Pneumonia	6	6		
Sinusitis	1****	2		
Candida (all)††††	16	15		
Chronic disseminated candidiasis	7	8‡‡‡‡		
Disseminated fungal infection	3	1		
Fungemia	6	6		
Zygomycetes‡‡‡	2	0		
Fusarium species§§§	1	0		
Trichosporon species†††	1	0		
Mold, not further identified¶¶¶	0	1		

- \* For the overall response rates of the composite primary end point, both stratified and observed responses are provided. For the rates of the component end points, such as survival for at least seven days after the completion of therapy, only the observed (unstratified) results are shown.
- † The 95.2 percent confidence intervals (CI) were adjusted for strata for the composite end point; the 95 percent confidence intervals are shown for the observed differences in the rates of the component end points.
- ‡ The difference was not calculated, since this end point was not a component of the prespecified primary analysis.
- § Nine patients (four in the caspofungin group and five in the liposomal amphotericin B group) were lost to follow-up before seven days after the completion of therapy had elapsed; their treatment was considered to have failed with respect to survival.
- ¶ In the caspofungin group, 6 patients had persistent fever, and 24 had suspected fungal infection; in the liposomal amphotericin B group, 9 had persistent fever, and 25 had suspected fungal infection. The dose of blinded study drug was escalated because of inadequate clinical response in 13 percent and 14 percent of recipients of caspofungin and liposomal amphotericin B, respectively.
- || Fungal infections were defined according to the criteria of the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.<sup>22</sup> To be considered proven or probable invasive fungal infections, histologic or microbiologic documentation was required for all filamentous fungal infections, microbiologic documentation for candidemia, and histologic documentation or characteristic radiologic features for chronic disseminated candidiasis.
- \*\* For the 14 available strains causing baseline candida infections in both treatment groups on testing for antifungal susceptibility, median minimal inhibitory concentration (MIC) values were as follows: caspofungin, 1.0 µg per milliliter (range, 0.5 to more than 8.0); amphotericin B, 0.50 µg per milliliter (range, 0.25 to 1.00). For aspergillus infections, the median MIC values were 0.25 µg per milliliter (range, 0.12 to 1.00) for caspofungin (eight isolates tested) and 1.0 µg per milliliter (range, 0.5 to 4.0) for amphotericin B (nine isolates tested). MIC values were determined according to National Committee for Clinical Laboratory Standards methods M27A for yeasts<sup>24</sup> and M38A for filamentous fungi.<sup>25</sup> One patient in the caspofungin group had breakthrough disseminated candidiasis and pulmonary aspergillosis; one patient in the liposomal amphotericin B group had breakthrough aspergillus sinusitis and pulmonary aspergillosis. Dashes indicate that no patients had the specified infection.
- †† Of the 12 patients in each group who had invasive aspergillosis, there were 7 proven and 5 probable cases in the caspofungin group and 8 proven and 4 probable cases in the liposomal amphotericin B group.
- ‡‡ Isolates included *Aspergillus candidus* (two), *A. flavus* (two), *A. fumigatus* (five), and aspergillus species not further identified (four). A patient may have had more than one isolate.
- §§ Isolates included *A. flavus* (five), *A. fumigatus* (one), *A. niger* (one), *A. terreus* (one), and aspergillus species not further identified (five). A patient may have had more than one isolate.
- ¶¶ One patient in this category had a mixed infection with *A. fumigatus* and fusarium species; in this patient, therapy failed.
- ||| Isolates included *Candida albicans* (three), *C. glabrata* (one), *C. krusei* (one), *C. parapsilosis* (one), and *C. tropicalis* (five). In one patient, the diagnosis of chronic disseminated candidiasis was based on radiographic findings alone.
- \*\*\*\* Isolates included *C. albicans* (four), *C. glabrata* (one), *C. krusei* (three), *C. parapsilosis* (one), *C. tropicalis* (two), and candida species not further identified (one).
- ††† The infection was fungemia.
- ‡‡‡ The infections included hepatic zygomycosis (one), pneumonia (one), and disseminated fungal infection (one).
- §§§ The infections included disseminated fusarial infection (two) and sinusitis (one).
- ¶¶¶ The infections included disseminated fungal infection (two) and pneumonia (one).
- ||| One patient in this category had a mixed infection with aspergillus species and *C. glabrata*.
- \*\*\*\* This patient had aspergillosis of the face, which probably extended from an infection of the maxillary sinus.
- †††† MIC values for the breakthrough isolates in the caspofungin group on testing for susceptibility ranged from 0.25 to more than 8 µg per milliliter (eight candida species) and from 0.06 to 0.5 µg per milliliter (five aspergillus species). MIC values for the tested breakthrough isolates in the liposomal amphotericin B group were 0.25 to 1 µg per milliliter (7 candida species) and 0.06 to 0.5 µg per milliliter (four aspergillus species).
- ‡‡‡‡ One patient had lesions compatible with chronic disseminated candidiasis on pathological examination, but the infection was documented only in the liver.



#### COMPONENTS OF THE PRIMARY END POINT

Rates of each component of the primary end point are shown in Table 2 and Figure 1. The data suggest that caspofungin-treated patients had better outcomes than the patients treated with liposomal amphotericin B with respect to three of the components: survival for at least seven days after treatment, successful treatment of baseline fungal infection, and absence of premature study discontinuation. Baseline fungal infections were diagnosed in 27 patients in each group; the most common were aspergillus pneumonia and candidemia. Of the patients with baseline fungal infections, more of those treated with caspofungin than of those treated with amphotericin B had a successful outcome. This was true for both invasive candidiasis and aspergillosis. The rate of occurrence of breakthrough fungal infections was similar in the two treatment groups. Among these patients, 48 percent receiving caspofungin and 35 percent receiving liposomal amphotericin B were classified as being at high risk. The proportion of patients who survived for at least seven days after therapy was greater in the caspofungin group than in the amphotericin B group. Premature study discontinuation because of toxicity or lack of efficacy occurred more often in the amphotericin B group than in the caspofungin group. The difference between the treatment groups was greatest with respect to discontinuations because of toxicity. Rates of resolution of fever in the setting of neu-

troponia were similar in the two treatment groups. However, as expected, the duration of neutropenia among high-risk patients was three to four days longer than that among low-risk patients ( $P < 0.001$ ). Rates of fever resolution were greater for those in the high-risk category than for those in the low-risk category but were similar in the two treatment groups: among the high-risk patients, the rates were 52.1 percent for those who received caspofungin and 50.0 percent for those who received liposomal amphotericin B, and among the low-risk patients, the rates were 37.3 percent and 38.8 percent, respectively.

#### SAFETY AND TOLERABILITY

Significantly fewer patients in the caspofungin group than in the liposomal amphotericin B group had an event associated with nephrotoxicity, an infusion-related event, or any drug-related adverse event or discontinued therapy because of a drug-related adverse event (Table 3). Although the rates of drug-related adverse events reported most frequently were similar in the two groups, several of them — chills, nausea, vomiting, a decrease in the serum potassium level, an elevation in the serum alkaline phosphatase level, and an elevation in the serum creatinine level — occurred less often with caspofungin than with amphotericin B.

#### MORTALITY

Overall study mortality, including the rate of death after the seven-day survival end point, was 10.8 percent (61 patients) in the caspofungin group and 13.7 percent (75 patients) in the liposomal amphotericin B group. The Kaplan–Meier analysis (Fig. 2) indicated that the proportion of patients who survived to the prespecified seven-day survival end point was greater in the caspofungin group than in the liposomal amphotericin B group (log-rank chi-square=4.05,  $P=0.04$ ). The causes of death were primarily complications of underlying diseases or infections and were distributed similarly in the two treatment groups. Among those who had a baseline fungal infection, the rate of death during the study was lower in the caspofungin group (11.1 percent [3 of 27 patients]) than in the amphotericin B group (44.4 percent [12 of 27]); in contrast, among patients with breakthrough fungal infections, mortality was similar in the two groups (34.5 percent in the caspofungin group [10 of 29 patients died] and 41.7 percent in the liposomal amphotericin B group [10 of 24 died]).

**Table 3. Results of the Safety Analyses.**

Variable	Caspofungin	Liposomal Amphotericin B	Difference (95% CI)*	P Value
	(N=564)	(N=547)		
	<i>percent of patients</i>		<i>percentage points</i>	
Nephrotoxicity†	2.6	11.5	-8.9 (-12.0 to -5.9)	<0.001
Infusion-related event‡	35.1	51.6	-16.4 (-22.2 to -0.7)	<0.001
Discontinuation of study therapy because of a drug-related adverse event	5.0	8.0	-3.1 (-6.0 to -0.02)	0.04
Any drug-related adverse event§	54.4	69.3	-14.9 (-20.5 to -9.2)	<0.001
Most commonly reported drug-related adverse events¶				
Clinical (any)	47.0	59.6	-12.6 (-18.4 to -6.8)	<0.001
Fever	17.0	19.4	-2.4 (-6.9 to 2.2)	
Chills	13.8	24.7	-10.9 (-15.5 to -6.2)	
Rash	6.2	5.3	0.9 (-1.8 to 3.6)	
Headache	4.3	5.7	-1.4 (-4.0 to 1.1)	
Hypokalemia	3.7	4.2	-0.5 (-2.8 to 1.8)	
Nausea	3.5	11.3	-7.8 (-10.9 to -4.7)	
Vomiting	3.5	8.6	-5.0 (-7.8 to -2.2)	
Dyspnea	2.0	4.2	-2.3 (-4.3 to -0.2)	
Flushing	1.8	4.2	-2.4 (-4.4 to -0.4)	
Laboratory (any)	22.5	32.0	-9.5 (-14.7 to -4.3)	<0.001
Increase in alanine aminotransferase	8.7	8.9	-0.1 (-3.5 to 3.2)	
Increase in aspartate aminotransferase	7.0	7.6	-0.6 (-3.7 to 2.4)	
Increase in alkaline phosphatase	7.0	12.0	-5.1 (-8.5 to -1.6)	
Decrease in potassium	7.3	11.8	-4.5 (-7.9 to -1.0)	
Increase in total bilirubin	3.0	5.2	-2.1 (-4.5 to 0.2)	
Increase in direct bilirubin	2.6	5.2	-2.6 (-5.3 to 0.2)	
Decrease in magnesium	2.3	2.6	-0.3 (-2.2 to 1.6)	
Increase in blood urea nitrogen	1.9	3.1	-1.2 (-3.9 to 1.5)	
Increase in creatinine	1.2	5.5	-4.3 (-6.4 to -2.1)	

\* CI denotes confidence interval. Negative values indicate a smaller proportion of patients in the caspofungin group.

† Nephrotoxicity (defined as a doubling of the serum creatinine level or, if the creatinine level was elevated at enrollment, an increase of at least 1 mg per deciliter [88  $\mu$ mol per liter]) was assessed in 547 patients in the caspofungin group and 522 in the liposomal amphotericin B group who had a creatinine clearance above 30 ml per minute.

‡ The most frequently reported infusion-related events were fever, chills, headache, nausea, and vomiting.

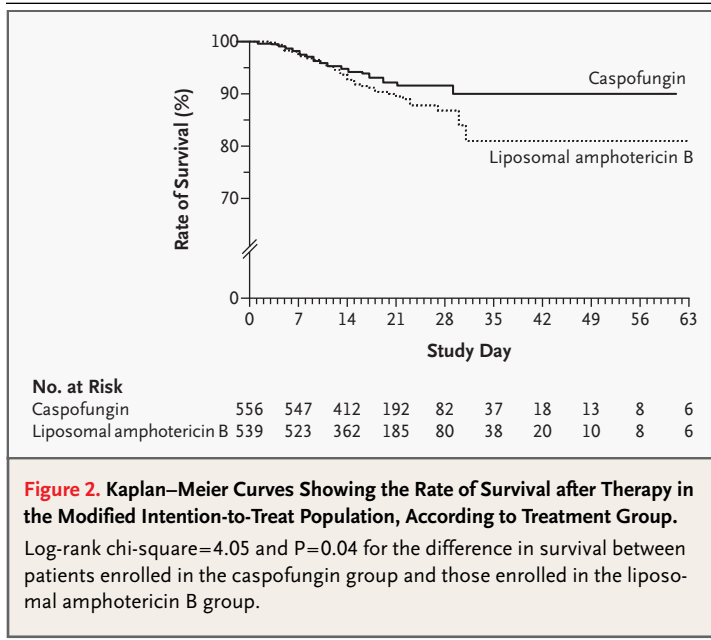
§ Events categorized as possibly, probably, or definitely related to study therapy were considered drug-related.

¶ The events listed are those with an incidence of at least 2 percent in at least one treatment group. For laboratory drug-related adverse events, only the results of tests performed on more than 100 patients are shown.

## DISCUSSION

This comparative trial, conducted in more than 1100 patients with neutropenia, showed that caspofungin was a suitable alternative to liposomal amphotericin B as empirical therapy and offered the advantages of safety, improved survival, and improved response rates in patients with invasive fungal infections. Thus, this large, double-blind, randomized, multicenter trial showed that an echinocan-

din has efficacy as empirical antifungal therapy in patients with persistent fever and neutropenia. More than 100 centers participated, allowing the study population to reflect the broad population of patients in North America and Europe. In addition, the adjudication committee classified all invasive fungal infections according to the new international criteria,<sup>22</sup> thus allowing worldwide interpretation of the data in adults. Patients younger than 16 years of age were not enrolled; because the plasma



pharmacokinetics of caspofungin in children differ from those in adults, further evaluation in children is warranted.<sup>26</sup>

The study is distinct from previous studies of empirical antifungal therapy in demonstrating improvements in survival and in the outcomes of baseline fungal infections and in placing an emphasis on patients with acute leukemia.<sup>4–8</sup> The high-risk nature of this study population is reflected by the designation of approximately 25 percent of the patients (more than 70 percent of whom had acute leukemia) as being at high risk and by the median duration of therapy of 10 to 11 days. Patients with breakthrough infections appeared to be a particularly high-risk group as compared with the overall study population. More of the patients who had breakthrough infections than of those in the modified intention-to-treat study population were classified as being at high risk.

The choice of dose of liposomal amphotericin B (3 mg per kilogram) was based on the dose of liposomal amphotericin B that has been approved by the Food and Drug Administration for empirical antifungal therapy in patients with persistent fever and neutropenia.<sup>5</sup> This dose was also used for comparison with voriconazole and with lipid formulations of amphotericin B in other randomized trials.<sup>4,6</sup>

That caspofungin, an echinocandin, was associated with an overall response similar to that

provided by a lipid formulation of amphotericin B represents an important benchmark in the understanding of comparative antifungal efficacy. Liposomal amphotericin B is better tolerated than conventional amphotericin B and is considered by many to be a more appropriate formulation for comparison. Nevertheless, caspofungin was similar in terms of overall success when assessed according to rigorously defined criteria. Moreover, the results of this study shed light on the properties of caspofungin. That caspofungin was active in treating baseline fungal infections (including pulmonary aspergillosis) and candidemia is a finding consistent with its efficacy in the primary treatment of candidemia and other deep-seated candidal infections and in salvage therapy for invasive aspergillosis in patients who do not have a response to amphotericin B.<sup>20,21</sup> Experimental data also demonstrate the in vitro and in vivo activity of caspofungin against *Candida albicans* and many candida species other than *C. albicans* and in animal models of invasive aspergillosis.<sup>13–16</sup> Caspofungin is fungicidal against actively growing cells of *Aspergillus fumigatus*.<sup>27</sup> Patients with breakthrough infections appeared to be a particularly high-risk group as compared with the overall, modified intention-to-treat study population. The improved safety and tolerability profile of caspofungin also permitted more patients to continue to receive the study therapy. The increased rates of renal and infusion-related toxicity associated with liposomal amphotericin B may add an additional burden in patients whose condition is already compromised. Thus, the outcome associated with caspofungin may be related both to its antifungal efficacy and to its safety profile.

In summary, caspofungin was as efficacious as liposomal amphotericin B in patients with persistent fever and neutropenia and was, overall, better tolerated than liposomal amphotericin B. Thus, caspofungin provides a new option for empirical antifungal therapy in these patients.

Supported primarily by individual institutional grants from Merck.

Dr. Baden reports having received grant support from Merck; Dr. Cornely consultation or lecture fees or grant support from Fujisawa, Gilead Sciences, Merck Sharp & Dohme, Pfizer, and Schering-Plough Research Institute; Dr. dePauw consultation or lecture fees from Fujisawa, Gilead, Merck Sharp & Dohme, Pfizer, and Vicuron; Dr. Maertens consultation or lecture fees from Gilead, GlaxoSmithKline, Fujisawa, Merck, Pfizer, and Schering-Plough; Dr. Donowitz consultation fees from Schering-Plough and grant support from Enzon, Fujisawa, and Merck; and Dr. Walsh grant support from Fujisawa and Merck.

We are indebted to Gail L. Woods, M.D., and Jeniffer Rabb for assistance in the preparation of the manuscript.

## APPENDIX

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