Refractory Aspergillus Pneumonia in Patients with Acute Leukemia

Successful Therapy with Combination Caspofungin and Liposomal Amphotericin

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BACKGROUND. Pulmonary aspergillosis and other invasive fungal infections (IFIs) commonly complicate the management of patients with acute leukemia. Standard amphotericin-based therapies may be ineffective for many patients and the available salvage agents (itraconazole and caspofungin) are reported to possess only moderate activity against resistant infections. Laboratory evidence suggests a synergistic interaction between amphotericin and caspofungin. The authors treated a group of patients with amphotericin-refractory IFIs with the combination of caspofungin and amphotericin (or liposomal amphotericin).

METHODS. A retrospective evaluation of patients with amphotericin-resistant IFIs was conducted. Diagnosis was based on clinical, radiographic, and when available, microbiologic data. Response to combination antifungal therapy was graded as either favorable or unfavorable. Favorable responses included improvement of both clinical and radiographic signs of fungal pneumonia. All other responses were graded as unfavorable.

RESULTS. Thirty patients were included in this analysis. Twenty-six patients had acute leukemia. Based on recently published criteria, the IFIs were classified as proven in 6 patients, probable in 4 patients, and possible in 20 patients. The median duration and dose of amphotericin monotherapy were 12 days (range, 4–65 days) and 7.8 mg/kg (range, 4.2–66.1 mg/kg), respectively. The median duration of combination therapy was 24 days (range, 3–74 days). Eighteen patients (60%) experienced a favorable antifungal response. Twenty patients with acute leukemia received combination therapy for fungal pneumonias arising during intensive chemotherapy treatments. Favorable responses were observed in 15 of these patients (75%), and antifungal response did not depend on the response of the underlying leukemia. Survival to hospital discharge was significantly better ($P < 0.001$) in patients having a favorable response. Mild to moderate nephrotoxicity was noted in 50% of patients, necessitating the substitution of liposomal amphotericin. Mild elevation of alkaline phosphatase levels occurred in 30% of patients. Caspofungin was temporarily withheld from one patient who developed moderate but reversible biochemical hepatotoxicity.

CONCLUSIONS. The antifungal combination of caspofungin and amphotericin can be administered safely to high-risk patients with hematologic malignancies. Although an absolute assessment of efficacy is limited by the design of this study, encouraging outcomes were noted for many patients. The authors plan to evaluate this regimen further in a randomized clinical trial. ***Cancer* 2003;97:1025–32.**

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Invasive pulmonary aspergillosis and other invasive fungal infections (IFI) commonly complicate the management of patients with hematologic malignancies. Approximately 36% of patients with acute leukemia may develop IFI.[1–7] These infections present most frequently as pneumonias that arise during induction therapy and are characterized by a persistent fever that is resistant to antibacterial drugs.[1,8,9] There has been a dramatic increase in the incidence of invasive aspergillosis during the 50 years following its initial description.[10] This increase has paralleled the development of improved supportive care for immunocompromised patients, which, in turn, has allowed the administration of more myelosuppressive chemotherapy regimens.[11] Although T-cell and macrophage function are important in the control of fungal disease, prolonged neutropenia remains the most significant risk factor for the development of these infections.[12] Specific antileukemic regimens[7] and the increasing use of central venous catheters may also be related to the increasing incidence.[13]

Amphotericin, which interacts with ergosterol in the fungal cell membrane, has been the mainstay of antifungal therapy and results in antifungal responses in 50% of patients.[14] Caspofungin, a member of the echinocandin class of antifungals, was recently approved for the treatment of invasive aspergillosis in patients who are intolerant or refractory to other agents. Its mechanism of action involves inhibition of the synthesis of β-(1,3)-D-glucan, a component of the fungal cell wall. Because of their distinct antifungal mechanisms, we postulated that the combination of caspofungin and amphotericin would act in an additive or synergistic manner. In vitro studies of this combination have already reported such interactions against *Aspergillus*, *Cryptococcus*, and *Fusarium* species.[15,16]

To our knowledge, no clinical data have been reported for combination antifungal therapy with caspofungin and amphotericin. Since the introduction of caspofungin, a group of patients at Memorial Sloan-Kettering Cancer Center (MSKCC) with amphotericin-resistant fungal pneumonias has been treated with a combination of caspofungin and amphotericin or liposomal amphotericin (AmBisome, Gilead Sciences, Foster City, CA). This retrospective analysis details our initial experience with this antifungal combination.

MATERIALS AND METHODS

Patients

All patients included in this study were treated at MSKCC for acute leukemia or other hematologic malignancies. Data obtained for this study were collected by retrospective chart review. Information collected from inpatient and outpatient charts included the underlying hematologic diagnosis; cytotoxic therapy and response; clinical, radiographic, microbiologic, and pathologic evidence of fungal infection; duration and dosage of amphotericin and caspofungin therapy; clinical, laboratory, and radiographic events; evidence of toxicity; and survival to hospital discharge. Patients were included as cases if they received the combination of caspofungin and amphotericin (either amphotericin B or liposomal amphotericin) for the treatment of amphotericin-refractory IFI. Patients receiving this combination of antifungals from March 2001 through December 2001 were identified through a query of the central pharmacy database. Because caspofungin was available from February 2001 to March 2001 (before its addition to the pharmacy database for central tracking), all admissions to the Leukemia Service during this period were reviewed to identify additional cases.

Diagnosis

Patients were included if they received the combination antifungal regimen for a presumptive diagnosis of IFI. The diagnosis of infection was based on clinical, radiographic, and microbiologic data. Clinical factors included high-risk patients with signs and symptoms of lower respiratory tract infection (e.g., dyspnea, cough, declining oxygen saturation) and persistent fever despite broad-spectrum antibacterial therapy. Radiographic evidence included plain radiography or a computed tomography scan that revealed new pulmonary infiltrates with or without pleural effusions. Cases were categorized by the probability of fungal infection according to a recently described classification system.[17] Microbiologic evidence was reviewed, when available, and included culture and/or microscopic evaluation (cytology or histopathology) of sputum specimens, bronchoalveolar washings, transbronchial biopsies, fine-needle pulmonary aspirations, and open lung biopsies.

All patients had fungal infections believed to be refractory to amphotericin on the basis of available clinical and radiographic evidence. Clinical signs of amphotericin resistance included persistent fever, worsening pulmonary symptoms, and deteriorating pulmonary function (e.g., oxygen saturation) despite an adequate course of amphotericin monotherapy. Radiographic studies revealing stable or worsening pulmonary infiltrates attributed to fungal infection were required. For the purposes of this analysis, a 7-day course of amphotericin was considered sufficient to document fungal resistance. Patients receiving less than a 7-day course of amphotericin monotherapy were included if combination antifungal therapy was initiated for rapid, life-threatening clini-

cal and radiographic progression of fungal disease. The administered amphotericin-equivalent dose was calculated for the period of monotherapy and for the entire duration of antifungal therapy according to the following equation: total amphotericin-equivalent dose = total amphotericin dose + (total liposomal amphotericin dose/5).

Response Grading

Antifungal response was based on clinical and radiographic evidence. Responses were graded as either favorable or unfavorable. Favorable responses included complete or partial resolution of all radiographic evidence of fungal infection accompanied by definitive improvement in associated clinical signs and symptoms. All other responses were graded as unfavorable.

Statistical Analysis

The 95% confidence intervals (95% CIs) were determined for reported proportions when the number of events and patients were sufficient to support the validity of the calculations. Chi-square analysis was used to evaluate the statistical significance of identified differences in comparative means and proportions.

RESULTS

Patients and Infections

Thirty-five patients receiving combination antifungal therapy were identified. Five patients were excluded because of inadequate follow-up or because the criteria for IFI and amphotericin resistance were not met. Thirty patients are included in this analysis and their diagnostic and clinical characteristics are summarized in Table 1. Twenty-six patients had acute leukemia including 18 patients with acute myeloid leukemia and 6 patients with acute lymphoblastic leukemia. Their median age was 60 years (range, 22–77 years). All patients had a presumptive diagnosis of invasive fungal pneumonia. In 20 patients, fungal pneumonia occurred in the setting of intensive chemotherapy treatments for acute leukemia.

Ten patients underwent invasive testing in an effort to document fungal pneumonia, including eight fiberoptic bronchoscopies (two with transbronchial biopsy), two fine-needle aspirations of the lung, and two open lung biopsies. *Aspergillus* was confirmed in three patients by cytopathology (two patients) and culture (one patient). *Penicillium* infection was documented by repeated blood cultures in one patient with clinical findings suggestive of disseminated fungal disease. One patient had candidemia (*Candida tropicalis*). In five additional patients, fungal forms were identified by culture and/or microscopic evaluation of pulmonary specimens. In one of these patients, yeast was identified on cytopathology of bronchoalveolar washings. The remaining cases were identified by cytopathology and/or culture of expectorated sputum specimens. In only two patients were potential nonfungal pathogens identified on the sputum culture of expectorated samples (parainfluenza virus 3 and *Enterobacter aerogenes*). Both patients are included in this analysis.

TABLE 1
Patient Characteristics (n = 30)

Demographics	No. of patients (%)
Gender	
Male	20 (67)
Female	10 (33)
Median age (yrs) (range)	60 (22–77)
Malignancy	
AML	18 (60)
ALL	6 (20)
Acute leukemia (other)[a]	2 (7)
Other[b]	4 (13)
Probability of fungal infection	
Proven	6 (20)
Probable	4 (13)
Possible	20 (67)

AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia.
[a] Includes one patient with biphenotypic acute leukemia and one patient with chronic myelocytic leukemia (CML) in the myeloblastic phase.
[b] Includes two patients with chronic lymphocytic leukemia, one patient with CML in the chronic phase, and one patient with myelodysplastic syndrome.

Categorization of patients according to the probability of IFI was based on host, clinical, and microbiologic factors. According to established criteria, the probability of fungal disease was graded as either proven, probable, or possible.[17] All patients were at high risk for fungal infection due to their underlying malignancy. Each had one or more host factors for invasive fungal disease (e.g., persistent fever despite broad-spectrum antibacterial support with or without prolonged neutropenia).[17–20] All patients had two or more minor clinical criteria for IFI: each had a new pulmonary infiltrate and each had at least one symptom of lower respiratory tract infection. Due to the retrospective nature of the study, clinical symptoms could not be reliably graded for their severity. Invasive fungal infection was categorized as proven in 6 patients, probable in 4 patients, and possible in 20 patients.

Impact of Neutropenia

Because of the increased inflammatory potential associated with granulocyte recovery in neutropenic pa-

tients, clinical and radiographic signs of pulmonary infection may worsen in the immediate period of blood count normalization independent of the inherent microbial resistance of the infecting mycosis. To assess the impact of neutrophil recovery as a potential confounding factor in the determination of amphotericin resistance, the incidence and timing of neutropenia were evaluated. Of the 20 patients who developed fungal pneumonia in the setting of intensive chemotherapy treatment for acute leukemia, 18 were neutropenic (absolute neutrophil count $<$ 500 cells per mm^3) when amphotericin monotherapy commenced. Neutrophil recovery never occurred in four of these patients. In the remaining 14 patients, neutrophil recovery occurred either before (4 patients; median, 7 days; range, 5–11 days) or after (10 patients; median, 6 days; range, 1–21 days) caspofungin was added. Combination antifungal therapy was initiated in the immediate period ($<$ 48 hours) of granulocyte normalization in only three patients. In two of these patients, the objective radiographic evidence supporting the assessment of amphotericin resistance was obtained more than 2 days before neutrophil recovery occurred. Resolution of neutropenia could not be excluded in the third patient as a potential confounding factor. Clinically relevant neutropenia was not observed in any of the 10 patients who had not received intensive chemotherapy for acute leukemia.

Antifungal Therapy

Seventeen patients received initial therapy with liposomal amphotericin because of advanced age or underlying renal insufficiency. The remaining 13 patients received initial therapy with amphotericin B, but ultimately 12 of these patients required a change to liposomal amphotericin because of amphotericin-related toxicity. In 10 patients, amphotericin B was changed to liposomal amphotericin before the initiation of caspofungin. In the remaining two patients, the modification was made after combination therapy was started (3 days and 6 days, respectively) because of renal insufficiency. Therefore, at the time caspofungin therapy commenced, 27 of 30 patients (90%) were receiving liposomal amphotericin.

All patients had fungal disease that progressed on amphotericin B or liposomal amphotericin. Nine patients (30%) had fungal disease that was also resistant to itraconazole. Of these, four had persistent fungal disease despite the combination of amphotericin and itraconazole. The median duration of amphotericin therapy before adding caspofungin was 12 days (range, 4–65 days). In 24 patients (80%), caspofungin was started only after the patient failed at least a 7-day course of amphotericin monotherapy. In six patients, however, fewer than 7 days of amphotericin monotherapy were administered (median, 5 days; range, 4–6 days). In each case, caspofungin was added early for rapid and life-threatening progression of fungal pneumonia. The median duration of combination antifungal therapy was 24 days (range, 3–74 days). None of the patients received leukocyte infusions or surgical therapy for fungal pneumonia.

The dose of amphotericin B was 1 mg/kg per day for the 13 patients initiated on this agent. Of the 17 patients who received liposomal amphotericin from the outset of treatment, 8 received an initial dose of 3 mg/kg per day, which was ultimately increased to 5 mg/kg per day. For six of these patients, the dose of liposomal amphotericin was modified before the addition of caspofungin (median, 3 days; range, 2–6 days). In the remaining two patients, the dose was increased after combined therapy was started (at 1 and 4 days following initiation of caspofungin). The median amphotericin-equivalent dose administered before the initiation of caspofungin was 0.7 g (range, 0.3–4.8 g) or 7.8 mg/kg (range, 4.2–66.1 mg/kg). The median total amphotericin-equivalent dose administered by the end of therapy or death was 2.5 g (range, 0.9–9.3 g). Caspofungin was administered by daily intravenous dosing (50 mg) after a single loading dose (70 mg) to 27 patients. The caspofungin dose was modified for hyperbilirubinemia (a 35-mg loading dose followed by a 30-mg daily dosing) in one patient. One patient received caspofungin, 70 mg daily, for 6 days before conversion to 50-mg daily dosing and another patient received only 50-mg daily dosing without a loading dose.

Treatment Outcomes

Overall, 18 patients (60%; 95% CI, 42–78%) experienced a favorable response to combination antifungal therapy. Six (20%) of these 18 patients achieved complete resolution of clinical signs and complete or near-complete resolution of radiographic evidence of fungal pneumonia. Five (83%) of the six patients with proven IFI achieved a favorable antifungal response. Of the patients with potentially confounding nonfungal pulmonary infections, the patient with *Enterobacter aerogenes* had a favorable response whereas the patient with parainfluenza virus 3 infection had an unfavorable outcome. Table 2 summarizes the antifungal treatment and outcomes for all patients in this study.

Of the 26 patients with acute leukemia, 20 patients developed invasive pulmonary aspergillosis following intensive chemotherapy treatments for their malignancy. Their characteristics and treatment outcomes are summarized in Tables 3 and 4. Ten of these pa-

TABLE 2
Overall Treatment/Results (n = 30)

Aspect	No. of patients
Median duration of amphotericin monotherapy (days)	12 (4–65)
Median dose of amphotericin monotherapy (mg/kg)	7.8 (4.2–66.1)
Median duration of combination antifungal therapy (days)	24 (3–74)
Median total amphotericin-equivalent dose (g)	2.5 (0.9–9.3)
Antifungal response (%)	
Favorable	18 (60)
Complete	6 (20)
Unfavorable	12 (40)
Survival to discharge (%)	
With favorable response (n = 18)	17 (94)
With unfavorable response (n = 12)	3 (25)

TABLE 3
Acute Leukemia/Intensive Chemotherapy Subgroup (n = 20)

Aspect	No. of patients (%)
Diagnosis	
AML	15 (80)
ALL	5 (20)
Leukemia status	
Newly diagnosed	10 (50)
Recurrent/refractory	10 (50)
Chemotherapy regimens used	
Anthracycline/cytarabine combinations	16 (80)
High-dose cytarabine containing	9 (45)
Response to combination antifungal therapy	
Favorable	15 (75)
Unfavorable	5 (25)

AML: acute myeloid leukemia; ALL: acute lymphoid leukemia.

TABLE 4
Antifungal Response According to Leukemia Response in Patients Receiving Intensive Chemotherapy for Acute Leukemia (n = 19)[a]

Aspect	No. of patients (%)
Leukemia response to chemotherapy	
Complete response	10 (53)
Refractory leukemia	9 (47)
Favorable antifungal outcome according to leukemia response	
Complete leukemia response (n = 10)	9 (90)
Refractory leukemia (n = 9)	6 (67)

[a] Leukemia response was evaluable in 19 of 20 patients with acute leukemia who received intensive chemotherapy.

tients had received reinduction therapy for recurrent or refractory leukemia. The remaining 10 patients received induction or consolidation therapy for newly diagnosed leukemia. Chemotherapy regimens included anthracycline combined with cytarabine in 16 of 20 patients (80%). High-dose cytarabine was administered to 10 patients. Leukemia response to chemotherapy was evaluable in 19 patients and was classified as either a complete response (CR) in 10 patients or as a nonresponse in 9 patients. A leukemia response was not necessary for a favorable antifungal response among patients with acute leukemia. This is because favorable responses were seen in 9 of 10 patients (90%) who achieved a CR and in six of nine patients (67%) with refractory leukemia (P = 0.25). Including the patient for whom leukemia response was not evaluable, 15 of 20 patients (80%; 95% CI, 62–98%) receiving intensive chemotherapy treatments for acute leukemia experienced a favorable response to the antifungal combination.

Poor outcomes was associated with both the timing of development of fungal infection and the underlying disease. Six patients with acute leukemia developed invasive fungal pneumonia prior to the administration of cytotoxic therapy or after recovery from it. Only 2 of these patients (33%) achieved a favorable antifungal response. Of the four patients with chronic leukemias or myelodysplastic syndromes, only one experienced a favorable response.

Six patients in this study received fewer than 7 days of amphotericin monotherapy before the initiation of combination antifungal therapy. The exclusion of these patients from the analysis did not affect the overall antifungal response rate (58% vs. 60%; P = 0.56) or the response rate for patients with acute leukemia receiving intensive chemotherapy (69% vs. 80%; P = 0.48).

Toxicity

Most of the toxicities observed in this cohort were consistent with the underlying diagnosis or complications of the administered cytotoxic therapy. Mild to moderate renal insufficiency was seen in 15 patients (50%; 95% CI, 32–68%) and was a common reason for the substitution of liposomal amphotericin for amphotericin B. Transient Grade 2 elevations of alkaline phosphatase levels were observed in nine patients (30%; 95% CI, 14–46%). Grade 3 elevation of alkaline phosphatase levels occurred in one patient and necessitated the temporary cessation of caspofungin (and other coadministered medications). No additional hepatotoxicity was noted in this patient and caspofungin therapy was reinitiated on improvement of the liver enzyme measurements. Subsequent deterioration of the liver enzymes was not noted. During the 31 days that caspofungin was withheld from this patient, radiographic progression of fungal pneumonia was noted. Upon reinstitution of combination antifungal therapy, this patient experienced a favorable antifungal response.

Nineteen patients (63%; 95% CI, 46–80%) sur-

vived to hospital discharge. As expected, patients whose fungal pneumonias did not respond favorably to antifungal therapy had markedly compromised survival. Of the 18 patients achieving a favorable response to antifungal therapy, 17 (94%) survived to discharge (1 patient died of sepsis). Only 3 of 12 patients (25%) having an unfavorable response survived to discharge ($P < 0.001$). Repeating the analysis of survival to hospital discharge with a landmark methodology (which included only patients receiving 7 or more days of caspofungin) did not affect the significance of this difference.

DISCUSSION

The management of refractory IFI in patients with hematologic malignancies remains a difficult problem. Despite therapy with amphotericin B, about 50% of patients with aspergillosis will fail primary therapy.[14] Fortunately, recent advances have increased the options available for refractory patients. The options available include itraconazole and caspofungin.

Several studies of invasive aspergillosis in patients with leukemia suggest that the ultimate prognosis depends on prompt administration of effective antifungal therapy.[21–24] Early initiation of active salvage therapy is crucial to secure the control of infection and ultimate survival of patients whose fungal disease is refractory to amphotericin.

Itraconazole, a triazole agent, is an alternative to amphotericin. Clinical trials in immunocompromised patients show that itraconazole is effective for some patients with invasive aspergillosis.[25,26] Favorable responses to itraconazole monotherapy for amphotericin-refractory infections are not well established. This is because published studies also include amphotericin-intolerant patients in their design.[25,26] These studies reported response rates that range from 39% to 63%. Therefore, it is unlikely that amphotericin-refractory patients will have a superior incidence of response compared with amphotericin-intolerant patients. Although itraconazole is less toxic than amphotericin,[27] its use is limited by drug interactions, variable and incomplete oral absorption in cancer patients, and the potential for decreased cardiac function. Because the toxicities do not overlap, itraconazole and amphotericin would be attractive agents for combination regimens to improve antifungal efficacy. Unfortunately, the lipophilic azoles may theoretically interfere with the action of amphotericin by interacting with ergosterol in the fungal cell membrane.[28] Evolving laboratory evidence suggests an antagonistic interaction between these two drugs.[29,30]

Caspofungin is approved for amphotericin-intolerant patients and for patients with amphotericin-resistant infections. However, for patients with amphotericin-refractory infections, caspofungin monotherapy yields only moderate response rates (36%).[31] Because achieving control of fungal disease in patients with leukemia is an important determinant of survival, efforts should be directed at improving antifungal responses, especially for patients failing primary therapy with amphotericin. Amphotericin and caspofungin act in different ways on the integrity of the fungal cell. Therefore, it is unlikely that these agents would be antagonistic. The limited preclinical data suggest that the combination has a synergistic fungicidal effect.[15,16]

An important finding in this study is the safety and feasibility of combining caspofungin with amphotericin in patients with hematologic malignancies and presumed IFI. Renal dysfunction was the most common toxicity and was primarily attributable to amphotericin. In the majority of cases, renal impairment was observed before the addition of caspofungin and was either reversed or stabilized by the substitution of liposomal amphotericin. Although two patients experienced nephrotoxicity while receiving caspofungin, the timing did not correlate with the initiation of combined therapy and their renal function improved following conversion to liposomal amphotericin. Hepatotoxicity, which manifested as asymptomatic liver enzyme elevation in 30% of patients, was potentially related to the amphotericin/caspofungin combination. However, only one patient (3%) required temporary discontinuation of caspofungin to allow resolution of liver toxicity. Ultimately, all patients either received the full-prescribed course of combination antifungal therapy or died of progressive pneumonia.

We observed an overall favorable antifungal response in 60% of patients in this analysis. Unfortunately, the study design precludes the definitive assessment of efficacy for combination therapy with caspofungin and amphotericin. An important limitation involves the inclusion of 20 patients categorized as "possible" IFI. Adequate microbiologic evidence was not collected for these patients to warrant categorization as proven infection because the necessary invasive testing was contraindicated by acute illness. However, given the typical host factors, clinical features, radiographic findings, and ultimate response to combination antifungal therapy, it is likely that many of these patients categorized as possible had IFI.

Invasive fungal infection was proven in only 6 of 30 patients (20%). Five (83%) of these six patients achieved a favorable response. Because of underlying illness, only 10 of 30 patients were able to undergo invasive procedures to document fungal infection. In most cases, the procedures were limited to fiberoptic

bronchoscopy without biopsy because of severe thrombocytopenia. This proportion is representative of the "standard of care" and the recognition that definitive diagnosis is difficult and poses substantial risk in this patient group. Fiberoptic bronchoscopy with culture or cytology of bronchial specimens is a relatively insensitive test for the confirmation of invasive pulmonary aspergillosis.[32] In addition, bronchoscopic biopsy is typically contraindicated in patients with acute leukemia and severe thrombocytopenia. Open lung biopsy is performed occasionally in patients requiring histopathologic or microbiologic confirmation of fungal infection, but this procedure has limited application in patients with acute leukemia.[33] Diagnostic invasive procedures are performed infrequently in patients with hematologic malignancies due to pancytopenia and other leukemia-related contraindications. This is particularly true for patients with acute leukemia who develop fungal pneumonia during intensive chemotherapy treatments.

Despite the limitations inherent in this analysis, we are encouraged by the outcome of the subgroup of patients receiving induction (or reinduction) therapy for acute leukemia. Of the 20 patients in this category, 15 (75%) had a favorable response to combination antifungal therapy. Neutrophil recovery did not impact the determination of amphotericin resistance, as worsening fungal pneumonia prompting initiation of caspofungin was noted during the immediate period of blood count normalization in only one patient. We also note that antifungal responses did not depend on the leukemic responses to chemotherapy, as a number of patients with refractory leukemia who never achieved functional neutrophil recovery had favorable antifungal outcomes. In contrast to this finding in most previous studies, residual leukemia has been associated with high rates of antifungal failure.[34] The finding that combined caspofungin and liposomal amphotericin can successfully treat fungal infections even in patients whose leukemias do not respond to cytotoxic therapy suggests that this is a highly active antifungal combination.

The current experience with caspofungin is limited. Comparisons between the results of this retrospective study and the available data for caspofungin monotherapy are difficult because of differences in the patient populations and because of variable criteria used for the diagnosis of fungal infection. The purpose of the current study was to assess the safety of amphotericin combined with caspofungin in patients with invasive fungal disease and to evaluate the efficacy of this combination in patients failing amphotericin due to resistant infections. Our data indicate that this combination is a safe and feasible option for the high-risk group of patients with hematologic disorders and presumed amphotericin-resistant fungal infections. If the combination of liposomal amphotericin and caspofungin acts in an additive or synergistic manner, it may be superior to therapy with caspofungin alone. To further assess this hypothesis, we plan to evaluate this combination regimen in a randomized clinical trial.

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