Liposomal Amphotericin B versus the Combination of Fluconazole and Itraconazole as Prophylaxis for Invasive Fungal Infections during Induction

Chemotherapy for Patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome

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BACKGROUND. Fungal infections are a major cause of morbidity and mortality in patients undergoing induction chemotherapy for acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). The authors evaluated the efficacy and toxicity of liposomal amphotericin B (L-AmB) compared with a combination of fluconazole plus itraconazole (F+I) as prophylaxis in this setting.

METHODS. Patients with newly diagnosed AML or high-risk MDS who were undergoing initial induction chemotherapy were randomized to receive either F+I (fluconazole 200 mg orally every 12 hours plus itraconazole tablets 200 mg orally every 12 hours) or L-AmB (3 mg/kg intravenously 3 times per week) in this prospective, open-label study.

RESULTS. Seventy-two L-AmB-treated patients and 67 F+I-treated patients were enrolled in the study. Of these, 47% of patients completed antifungal prophylaxis without a change in therapy for proven or suspected fungal infection. Three patients in each arm developed a proven fungal infection. Twenty-three percent of the L-AmB-treated patients and 24% of the F+I-treated patients were changed to alternative antifungal therapy because of persistent fever (P value not significant). Nine percent of the L-AmB-treated patients developed pneumonia of unknown etiology compared with 16% of the F+I-treated patients (P value not significant). Increases in serum creatinine levels to > 2 mg/dL (20% for the L-AmB arm vs. 6% for the F+I arm; $P = 0.012$) and increases in serum bilirubin levels to > 2 mg/dL (43% vs. 22%, respectively; $P = 0.021$) were more common with L-AmB. Infusion-related reactions were noted in five L-AmB-treated patients. Responses to chemotherapy and induction mortality rates were similar for the two arms.

CONCLUSIONS. L-AmB and F+I appear similar in their efficacy as antifungal prophylaxis during induction chemotherapy for patients with AML and MDS. L-AmB was associated with higher rates of increased serum bilirubin and creatinine levels.
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Suspected or proven fungal infections remain a major cause of morbidity and mortality in patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) undergoing induction chemotherapy. Although fluconazole prophylaxis has been found effective in the prevention of fungal infections in patients undergoing bone marrow transplantation,[1,2] results of

studies of prophylaxis in patients with AML are contradictory (some studies are positive,[3–8] whereas others are negative[9–11]) and often are limited by enrollment of mixed patient populations. Yoshinobu et al. performed a meta-analysis (16 trials that included 3734 patients) to evaluate the efficacy of fluconazole prophylaxis during chemotherapy-induced neutropenia. Although fluconazole was effective in reducing superficial fungal infections, in patients who did not undergo bone marrow transplantation, neither systemic fungal infections nor fungal-related deaths were affected.[11] Three of the larger studies, however, strongly suggested a role for prophylaxis. First, a comparison of fluconazole (400 mg per day) with placebo in 257 patients with acute leukemia (70% had AML) demonstrated that fluconazole produced a statistically nonsignificant reduction in the rate of invasive fungal infections from 8% to 4%.[6] Itraconazole oral solution; 2.5 mg/kg every 12 hours) reduced the rate of invasive fungal infections relative to placebo from 33% to 24% ($P = 0.035$) in a group of 405 adult patients (75% had acute leukemia).[3] Finally, a comparison of fluconazole 100 mg/day with itraconazole 2.5 mg/kg every 12 hours in 445 patients (70% had AML, and 16% had ALL) found results favoring itraconazole, especially for patients with aspergillosis.[4]

These results are logical and consistent. Itraconazole is superior to fluconazole against *Aspergillus* infections;[12] however, itraconazole capsules are absorbed poorly, thus necessitating the determination of serum levels to ensure adequate absorption. Consequently, itraconazole capsules alone may not always provide reliable prophylaxis. Conversely, fluconazole is highly active against most species of *Candida* and is absorbed reliably. Thus, a logical strategy may be to combine these agents as prophylaxis.

Amphotericin B is another logical avenue for antifungal prophylaxis, although its use is limited by its significant toxicities. Liposomal amphotericin B (L-AmB) is a lipid-associated preparation of amphotericin B that has demonstrated less toxicity compared with conventional amphotericin B.[12]

We previously observed that a combination of fluconazole plus itraconazole (F+I) appeared to reduce the incidence of suspected or proven fungal infections relative to historic data with fluconazole alone (unpublished data). In this prospective, randomized study, we have compared the efficacy and toxicity of the combination of F+I with L-AmB as antifungal prophylaxis in patients with AML or MDS undergoing induction chemotherapy.

MATERIALS AND METHODS

Patients

Patients were eligible for the study if they 1) were age $\geq$ 15 years, 2) were undergoing initial induction chemotherapy for the treatment of AML or MDS, 3) had a serum creatinine level $<$ 3.0 mg/dL, and 4) had no clinical or other evidence of a systemic fungal infection at enrollment. After enrollment, patients were deemed unevaluable if 1) they received $<$ 5 days of study therapy for reasons other than drug toxicity or 2) information obtained within the first 24 hours of study therapy documented the presence of a fungal infection (as defined below). Patients with a history of anaphylaxis attributed to amphotericin B or azoles and patients with moderate or severe liver disease (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase levels $>$ 5 times the upper limits of normal or total bilirubin $>$ 3.0 mg/dL) were excluded. The M. D. Anderson Investigational Review Board approved all study procedures. Informed consent of the patient or a legally authorized representative was obtained for each patient.

Study Protocol

Eligible patients were randomized using a 1:1 randomization schedule generated by the Statistics/Research Computing Department of Fujisawa USA, Inc. (Deerfield, IL) to receive L-AmB or F+I. Patients who were randomized to the F+I arm received 200 mg fluconazole (capsules) every 12 hours and 200 mg of itraconazole (capsules) every 12 hours. Itraconazole was taken with a full meal to ensure maximal absorption. H_2 blockers and proton pump inhibitors were avoided in patients who received F+I. For patients who were randomized to the L-AmB arm, an intravenous dose of 3.0 mg/kg was administered over 2–4 hours 3 times per week. Because L-AmB has a long terminal half-life, it was expected that intermittent dosing (i.e., 3 mg/kg 3 times per week) would be effective. Other reasons that were taken into consideration were the convenience and ease of administration and the lower cost. Patients who were randomized to the L-AmB arm received acetaminophen 650 mg orally, diphenhydramine 25 mg intravenously, and meperidine 25 mg intravenously as premedication. The use of intravenous hydrocortisone 50 mg was optional for patients with chills. Prophylaxis was continued until 1) the absolute neutrophil count was $> 0.5 \times 10^9$/L on 2 consecutive days, 2) the patient achieved a complete response or failed induction chemotherapy for AML or MDS, 3) the patient developed a proven or suspected systemic fungal infection, or 4) the patient developed unacceptable toxicity to the study drug. In addition to

antifungal prophylaxis, all patients received antibacterial and antiviral prophylaxis with oral levofloxacin 500 mg daily and oral valacyclovir 500 mg daily.

Definition of Fungal Infection

Proven fungal infections were diagnosed by the presence of positive culture for fungus in the blood, pulmonary tissue, respiratory secretions, sinuses, soft tissues, or other organs in association with symptoms and signs of infection. All infections in this category had to meet the criteria for either proven or probable infection according to recently published definitions.[13] When fever persisted for 3 days beyond a change of antibacterial therapy without microbiologic support for a fungal infection, two categories of possible fungal infection were used. First, patients with radiographic findings of pneumonia were categorized with pneumonia of unknown etiology (PUE)—these patients would meet the published criteria for possible fungal pneumonia.[13] If fever persisted without any localizing signs, then the patient was categorized with fever of unknown origin (FUO).

Statistical Analysis

Sample sizes per treatment arm were calculated based on the ability to detect treatment differences in success rates (no development of proven or presumed systemic fungal infections) with 90% power. Based on data from published studies, a success rate of 55% with F+I was assumed. A sample size of 144 evaluable patients (72 evaluable patients per treatment arm) who complete the prophylaxis regimen was required to detect a difference of 25% (improvement, 80% vs. 55%) in success rates between the two treatment arms using a two-tailed test of significance with $\alpha = 0.05$.

Survival was defined as the interval from the initiation of chemotherapy until the date of death from any cause or censoring. Time to fungal infection was defined as the interval from the initiation of study prophylaxis until the date of onset of proven or possible fungal infection or until the end of observation for such events. Survival distribution curves were estimated by using the Kaplan–Meier method and were compared using the log-rank test. Multivariate analyses were performed using a Cox proportional hazards model. Stepwise, backward regression was used to find the most significant factors. Univariate analysis using Fisher exact tests or *t* tests, as appropriate, was employed to evaluate potential imbalance of the risk factors between the two treatment arms. To predict the event of fungal infection and the status of complete response to chemotherapy, we also fit multivariate logistic regression models. The best models were determined by a backward selection procedure. All *P* values presented are two-sided, and a P value < 0.05 was considered statistically significant. Statistical analyses were carried out using SAS software (version 6.12 for Windows; SAS Institute, Inc., Cary, NC) and S-plus 2000 (MathSoft, Inc., Seattle, WA).

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%) L-AmB	No. of patients (%) F+I	*P* value
No. of patients	70 (51)	67 (49)	—
Age(yrs)			
Median	64	57	—
Range	36–83	19–84	0.006
Gender			
Male	42 (60)	41 (61)	—
Female	28 (40)	26 (39)	NS
Underlying disease			
AML	53 (76)	43 (64)	—
MDS	17 (24)	24 (36)	NS
Zubrod performance status			
0–2	70 (100)	65 (97)	—
≥ 3	—	2 (3)	NS
ERM score			
Median	0.19	0.15	—
Range	0.0–0.85	0.0–0.80	NS
Antecedent hematologic disease[a]	41 (59)	27 (40)	0.041
Protective environment	54 (77)	47 (70)	NS
Neutropenia on admission	32 (46)	34 (51)	NS
Nonfungal infection at start of study[b]	13 (19)	12 (18)	NS
Duration of neutropenia (days)			
Median	11	12	NS
Range	0–24	0–32	NS

L-AmB: liposomal amphortericin B; F + I: fluconazole and itraconazole; NS: not significant AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; ERM: early risk of mortality.[22]

[a] Documented antecedent hematologic disorder (i.e., anemia, high white blood cell count, low plate count), as defined previously.[21]

[b] Includes pneumonia, septicemia, fever of unknown origin, cellulitis, otitis, and urinary tract infection.

RESULTS

Patient Characteristics

One hundred thirty-nine patients with AML (98 patients) or MDS (41) were randomized. One patient was excluded from the analysis because he did not receive study drug, and a second patient was excluded because of possible fungal pneumonia documented within 24 hours of enrollment. Of the remaining 137 patients, 70 patients received L-AmB prophylaxis, and 67 patients received F+I prophylaxis (Table 1). The two patient groups differed in only two respects: First, the patients in the F+I arm were younger compared with the patients who were randomized to the L-AmB arm ($P = 0.006$). Conversely, 60% of the L-AmB-treated patients had a history of an unfavorable antecedent hematologic disease ($P = 0.032$).

TABLE 2
Response to Induction Chemotherapy

	No. of patients (%)	
Response	**L-AmB**	**F + I**
No. of patients	70 (100)	67 (100)
Complete response	42 (60)	38 (56)
Resistant	18 (26)	21 (31)
Died	10 (14)	8 (12)

L-AmB: liposomal amphortericin B; F + I: fluconazole and itraconazole.

TABLE 3
Outcome of 49 Patients with Fever of Unknown Origin or Pneumonia of Unknown Etiology

Prophylaxis	No. of patients	Treatment/dose	Outcome
L-AmB	21	Ambisone (5–10 mg × kg/day)	Four of 22 patients died within 30 days at the last prophylactic doses (2 with persistent leukemia and sepsis; 1 failure; 1 lost to follow-up)
L-AmB	1	ABLC (5 mg × kg/day)	No death due to proven/probable fungal infection
F+I	18	Ambisone (5–10 mg × kg/day)	Six of 27 patients died within 30 days at the last prophylactic doses (4 with persistent leukemia and sepsis; 2 with cardiovascular complications)
F+I	8	ABLC (5 mg × kg/day)	No death due to proven/probable fungal infection
F+I	1	No further antifungal treatment; FUO responded to antibacterial treatment	No death due to proven/probable fungal infection

L-AmB: liposomal amphortericin B; ABLC: amphotericin B lipid complex; F + I: fluconazole and itraconazole; FUO: fever of unknown origin.

The majority of patients in both study arms received topotecan, cyclophosphamide, and cytarabine as induction chemotherapy (69% of patients in the L-AmB arm and 72% of patients in the F+I arm). The complete response rate to chemotherapy was identical in the two groups (Table 2).

Outcome

Overall, 66 of 137 patients (48%) completed their antifungal prophylaxis, including 34 of 70 patients (49%) in the L-AmB arm and 32 of 67 patients (48%) in the F+I arm ($P = 1.000$). Twenty-two of 70 patients (31%) in the L-AmB arm had their initial antifungal therapy altered for FUO (16 patients) or PUE (6 patients) compared with 27 of 67 patients (40%) in the F+I arm (16 patients with FUO and 11 patients with PUE; $P = 0.291$). The clinical outcome of these patients is shown in Table 3.

TABLE 4
Clinical Outcome

	No. of patients (%)	
Characteristic	**L-AmB**	**F+I**
No. of patients enrolled	70 (100)	67 (100)
Completed prophylaxis[a]	34 (49)	32 (48)
FUO	16 (23)	16 (24)
PUE	6 (9)	11 (16)
Withdrawn from prophylaxis for toxicity	10 (14)	5 (8)
Discontinued for other reason[b]	1 (1)	0 (0)
Documented fungal infection	3 (4)	3 (5)
C. glabrata	2	—
C. parapsilosis	1	—
C. tropicalis	—	1
A. fumigatus	—	2

L-AmB: liposomal amphortericin B; F + I: fluconazole and itraconazole; FUO: fever of unknown origin; PUE; pneumonia of unknown etiology.

[a] Remained on initial randomized antifungal prophylaxis until recovery from neutropenia.

[b] The drug was stopped after one dose because of worsening pneumonia.

Three patients in each arm developed a documented fungal infection (Tables 4, 5). In the multivariate logistic regression analysis, no statistically significant predictor of fungal infection was found.

There were 10 deaths in the L-AmB arm and 8 deaths in the F+I arm. One of these deaths in each arm was due to a fungal infection in a patient who also failed to recover from neutropenia (Table 5). Survival by treatment group was similar (Fig. 1). The covariate-adjusted multivariate analysis showed that age was associated significantly with an increased risk of death ($P = 0.006$), although that survival did not differ between the two treatment arms ($P = 0.446$).

In an additional analysis, patients with preexisting, presumed or proven, nonfungal infections were excluded, because the preexisting infection may have masked a fungal infection. Among 112 such patients (57 patients in the L-AmB arm and 55 patients in the F+I arm), there were 3 patients in each arm with proven fungal infections ($P = 0.968$) and 25 patients in the L-AmB arm and 20 patients in the F+I arm with new bacterial infections ($P = 0.418$). The log-rank test did not show a significant difference in time to failure in this analysis, with a median time to failure of 18

TABLE 5.
Patients with Documented Fungal Infections

Patient	Age (yrs)	Prophylaxis	Culture (day of culture relative to start of prophylaxis)	Days On prophylaxis	Site of infection	Days with ANC < 500/mm^3	Outcome
1	69	L-AmB	*C. glabrata* + *C. tropicalis* (Day 11)	9	Cellulitis	12	Changed to L-AmB + itraconazole recovery from neutropenia, Cured
2	82	L-AmB	*C. glabrata* (Day 3)	5	Blood	13	Changed to L-AmB; never recovered from neutropenia; died
3	78	L-AmB	*C. parapsilosis* (Day 4)	8	Blood	95	Changed to L-AmB; recovered from neutropenia; cured
4	65	F+I	*A. fumigatus* (Day 17)	14	Sinuses	10	Changed to L-AmB + AmB by inhalation + itraconazole; recovered from neutropenia; cured
5	61	F+I	*C. tropicalis* (Day 12)	12	Catheter and blood	21	Changed to L-AmB and then ABLC; never recovered from neutropenia; died
6	50	F+I	*A. fumigatus* (Day 18)	17	Skin nodule	47	Disease proven by culture of biopsy; changed to ABLC; recovered from neutropenia; cured

ANC: absolute neutrophic count; L-AmB: liposomal amphortericin B; F + I: fluconazole and itraconazole; ABLC: amphotericin B lipid complex.

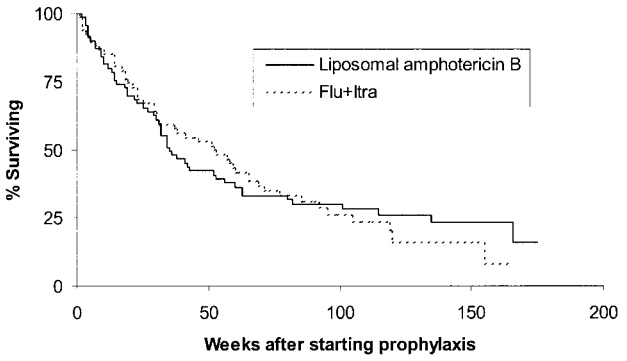

FIGURE 1. Survival curves indicating the proportion of patients who survived over time. The two curves did not differ according to the log-rank test ($P = 0.881$). The median survival was 35 weeks (range, 31–60 weeks) for patients who were treated with liposomal amphotericin B and 52 weeks (range, 30–71 weeks) for patients who were treated with fluconazole plus itraconazole (Flu+Itra).

days and 16 days for the L-AmB and F+I arms, respectively.

Adverse Events

Fifteen patients, including 10 patients in the L-AmB arm and 5 patients in the F+I 5 arm, were withdrawn from the study because of drug-related toxicities ($P = 0.276$; Tables 4, 6). Seven of 10 patients in the L-AmB arm were changed to F+I, and the other 3 patients received amphotericin B lipid complex. In the F+I arm, two patients were kept on fluconazole alone, one patient was changed to L-AmB, one other patient received amphotericin B lipid complex, and one patient did not receive further prophylaxis. The L-AmB-treated patients more often developed increased bilirubin levels ($P = 0.012$), increased creatinine levels ($P = 0.021$), and infusion-related symptoms ($P = 0.058$).

DISCUSSION

In this study, L-AmB and the combination of F+I showed comparable efficacy as prophylaxis against fungal infections in patients with AML or MDS undergoing induction chemotherapy. Responses to induction chemotherapy and survival rates also were similar in the two groups, although the patients who received L-AmB had an increased risk of death.

The combination of F+I was well tolerated. Prophylaxis with L-AmB at 3 mg/kg 3 times per week was associated with somewhat higher rates of toxicity, but this therapy also generally was well tolerated. Comparable results were seen in prior studies of L-AmB at doses of 2 mg/kg 3 times per week[14] and 1 mg/kg per day.[15]

Overall, 66 of 137 patients (48%) completed their antifungal prophylaxis: 34 of 70 patients in the L-AmB arm (49%) and 32 of 67 patients in the F+I arm (48%). The 95% confidence interval for the true difference between these rates was from −0.18 to 0.16. Because this interval included 0, we cannot say that the two treatments were different with respect to the completion rates, but we also cannot say that the two treatments yield equivalent completion rates.

In general, the incidence of documented fungal infection in our study was similar both to the rate of 1–4% for patients receiving prophylaxis in other stud-

TABLE 6
Adverse Events

	Grade ≥ 1 (%)			Grade ≥ 3 (%)		
Event	**L-AmB**	**F+I**	***P* value**	**L-AmB**	**F+I**	***P* value**
Elevated bilirubin level	30 (43)	15 (22)	0.012	4 (6)	3 (4)	0.772
Elevated creatinine level	14 (20)	4 (6)	0.021	—	1 (1)	0.298
Rash	—	2 (3)	NS	—	—	—
Gastritis	—	1 (1)	NS	—	—	—
Back pain	1 (1)	—	NS	—	—	—
Dyspnea and rash	—	1 (1)	NS	—	—	—
Infusion-related symptoms[a]	5 (7)	—	0.058	5 (7)	—	0.058

L-AmB. liposomal amphortericin B; F+I: fluconazole and itraconazole; NS. not significant.

[a] Infusion-related symptoms. dyspnea, chills, or fever. Other toxicities were scored using the National Cancer Institute Common Toxicity Criteria (version 2.0; last revised, 4/30/1999; published online at http://ctep.info.nih.gov/CTC3/default.htm).

ies that focused on patients with leukemia[4,16,17] and to the 3–6% rate observed with prophylaxis in studies that focused on patients undergoing bone marrow transplantation.[2,15] Historically, the most frequent cause of death in patients with AML and MDS in our institution has been aspergillosis.[18,19] In this study, we had only a 1.5% rate of documented mold infections (two patients with aspergillosis), and this low rate was very encouraging. It is noteworthy that both patients with aspergillosis were in the F+I arm. We feel that this may have been the result of decreased itraconazole absorption. Other possible explanations include be the lack of patient compliance or the need for higher itraconazole blood levels in this type of patient. Our 23–24% rate of FUO with prophylaxis was similar to the rates of 14–29% found in one previous report[17] but higher compared with the 3–9% rate found in prophylaxis studies done both by others[15] and at our institution.[7] We also observed a 12% incidence of PUE. Because PUE and FUO may be due either to a nonfungal infection or to a partially controlled fungal infection, it is possible that prophylaxis served principally to limit the extent of fungal infection and, thus, reduced our ability to make a firm diagnosis. The current lack of sensitive serodiagnostic tools for fungal infections further limits our ability to draw conclusions from this group.

L-AmB was associated with a greater frequency of increases in creatinine and bilirubin levels compared with the azole-based regimen. The increase in creatinine is a risk for all amphotericin B-based regimens, and our results were similar to those reported by others.[15] Kelsey et al. reported bilirubin increases with the use of L-AmB, but the changes were not relevant clinically.[14] Walsh et al. noted increases in serum alkaline phosphatase and total bilirubin levels in a series of patients who were treated with L-AmB,[20] but those authors concluded that concomitant chemotherapy agents, preparative regimens for bone marrow transplantation, and the presence of graft-versus-host diseases or venoocclusive diseases more likely were related to these changes rather than L-AmB. The use of intensive chemotherapy along with multiple concomitant agents likewise makes it difficult to relate hepatic dysfunction to any single agent in our study.

Our 7% rate of infusion-related symptoms also was similar to the 7% rate reported by Kelsey et al. using 2 mg/kg three times per week[14] and the 5% rate reported by Walsh et al.[20] for doses of 1.0–7.5 mg/kg daily. Five of our patients were withdrawn from the study because of infusion-related symptoms, all of whom presented with fever, dyspnea, and chills. We did not attempt to increase the premedication in these patients and, thus, do not know whether more aggressive use of such treatments would have permitted continued therapy.

The limitations of this study include the lack of itraconazole blood level measurements, the limited numbers of autopsies (of 18 patients who died, only 1 patient had an autopsy), and the relatively small numbers of patients. However, our data suggest that L-AmB and F+I are comparable as prophylaxis for patients with fungal infections in this setting. The combination of azoles was associated with lower toxicity and may be used in patients who can tolerate oral medications. L-AmB is a good alternative for patients who have absorption problems or who cannot receive oral medications.

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