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Weekly liposomal amphotericin B as secondary prophylaxis for invasive fungal infections in patients with hematological malignancies

LIZBETH CAHUAYME-ZUNIGA[*], **RUSSELL E. LEWIS**[*,†], **VICTOR E. MULANOVICH**[*,†], and **DIMITRIOS P. KONTOYIANNIS**[*,†]

[*]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[†]College of Pharmacy, University of Houston, Houston, Texas, USA

Summary

No reported studies evaluating the efficacy and safety of weekly liposomal amphotericin B as secondary prophylaxis in leukemic patients with invasive fungal infections (IFIs) exist. This approach was associated with frequent relapse of IFIs (36%) and kidney injury (36%) in the retrospective review of our experience with 14 such patients (2003–2009).

Keywords

Liposomal amphotericin B; secondary prophylaxis; invasive fungal infection

Introduction

Patients with hematologic malignancies are at high risk for severe IFIs, especially invasive pulmonary aspergillosis [1–3]. Despite advances in antifungal treatment, these patients remain at high risk of IFI relapse [2,3]. There is no consensus on the optimal secondary antifungal prophylaxis in these patients and such decisions are based mainly on results from primary prophylaxis randomized trials that enrolled a rather selected patient population [4].

Although oral broad-spectrum triazoles are a logical choice for secondary prophylaxis for the majority of patients with history of invasive mold infections, not all patients are eligible due to hepatic dysfunction, drug-drug interactions, noncompliance, or inability to pay [3–5]. Therefore, there is still need for parenteral broad-spectrum secondary prophylaxis in a subset of such patients in the clinical practice.

Amphotericin B (AmB) has the broadest spectrum of activity of all available parenteral antifungal agents [5]. However, most of the primary prophylaxis studies using conventional AmB deoxycholate, showed considerable toxicity including infusion reactions and nephrotoxicity [6–8]. Liposomal AmB (L-AmB) is better tolerated than the conventional drug, but its advantages in the prophylactic setting remain unclear [9–11]. Specifically,

Correspondence: Dimitrios P. Kontoyiannis, MD, Department of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Tel: +1 713 792 6237; fax: +1 713 745 6839; dkontoyi@mdanderson.org.

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studies evaluating L-AmB in primary prophylaxis for IFIs in patients with hematological malignancies found no clinically significant efficacy at a dosage of 1 mg/kg/day [10] or 2 mg/kg given three times weekly [11]. Recently, a study by Gubbins and colleagues showed that treatment with infusion of a single 15-mg/kg dose or a weekly dose of 7.5 mg/kg of L-AmB produced sufficient concentrations in serum and buccal mucosa tissue in adult patients undergoing stem cell transplantation [12]. Thus, L-AmB weekly infusion is likely to be logistically convenient for the outpatient cancer population who is receiving ongoing immune suppression with multiple and complicated regimens. Two studies evaluated the efficacy and safety of once-weekly L-AmB as primary prophylaxis for IFIs in patients with hematological malignancies [5,9]. Specifically, El Cheikh and colleagues administered 7.5 mg/kg L-AmB weekly in 21 patients receiving high-dose corticosteroids for acute graft-versus-host disease after allogeneic stem cell transplantation; no death were attributed to fungal infection, only one patient developed invasive pulmonary aspergillosis two months after L-AmB was stopped and seven patients (33%) discontinued LAmB owing to drug-related adverse events [5]. Also, Cordonnier and co-workers concluded that primary prophylaxis with L-AmB at a high dosage (10 mg/kg/week) was well tolerated during induction or consolidation chemotherapy in 21 patients with acute leukemia with 3 of these patients developing IFIs breakthrough [9].

The encouraging experience with the use of weekly L-AmB as primary prophylaxis for IFIs [5,9] indicates that such strategy may be also useful in secondary prophylaxis. We report our experience with L-AmB used as secondary prophylaxis for IFIs in 14 patients with hematological malignancies who needed further courses of chemotherapy or underwent stem cell transplantation.

Methods

An Institutional Review Board-approved retrospective medical record review of patients who received L-AmB at The University of Texas MD Anderson Cancer Center identified patients who received weekly L-AmB as secondary prophylaxis for IFIs over a 6-year period (2003–2009). The decision to implement that secondary prophylaxis strategy was made by the treating physician for a variety, at times multiple reasons (e.g., convenient outpatient dosing schedule, pre-existing liver dysfunction, gastrointestinal intolerance of azoles, lack of insurance coverage for oral triazoles). Patients who received concomitantly inhaled AmB or other systemic antifungals were excluded. Diagnosis of prior IFI was based on the revised definitions of IFI from the European Organization for Research and Treatment of Cancer and the Infectious Diseases Mycoses Study Group [13]. Acute kidney injury was defined according to Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE) criteria by the Acute Dialysis Quality Initiative [14]. Secondary prophylaxis was defined as weekly administration of L-AmB at 5–10 mg/kg during a period of high risk for infection to prevent IFI relapse. Complete response of IFI prior to L-AmB use as secondary prophylaxis was defined as resolution of all attributable symptoms and signs of disease and radiological abnormalities and mycological or biomarkers evidence of eradication of disease [15]. Partial response of IFI was defined as improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden as determined by using a galactomannan assay [15]. The primary end points for secondary prophylaxis were the absence of proven or probable breakthrough IFI and premature withdrawal from the study as a result of L-AmB toxicity [16].

Results

We identified 14 eligible patients (9 men and 5 women; median age, 55 years [range, 23–73 years]). The characteristics of these patients are listed in Table 1. Two patients underwent

allogeneic stem cell transplantation before the development of IFI. Most of the patients (12 [86%]) had prior fungal pneumonia. The diagnostic certainty for IFI was proven in seven cases, probable in two cases, and possible in five cases. We identified the implicated pathogen in nine patients: aspergillosis in four patients, mucormycosis in three patients, invasive disseminated candidiasis in one patient, and fusariosis in one patient.

Twelve patients (86%) received subsequent cytotoxic chemotherapy (seven salvage and five maintenance) while undergoing secondary prophylaxis with weekly L-AmB. Neutropenia developed after in six of these patients (range duration, 1 week to 4 months). Of the two remaining patients; one received chronic corticosteroids, whereas another received tacrolimus.

The initial treatment of IFI in 12 patients (86%) prior to secondary prophylaxis consisted of L-AmB alone or in combination with another antifungal (caspofungin, anidulafungin, voriconazole, or posaconazole). The remaining two patients received caspofungin plus voriconazole. All 14 patients had either a partial (6) or complete (8) response of his or her IFI to the initial treatment prior to initiation of weekly prophylaxis with L-AmB.

The weekly L-AmB doses ranged from 5 to 10 mg/kg. Each patient received at least four doses (median dose, 7 mg/kg). The total treatment durations ranged from 14 to 128 days (median, 28 days; mean, 43 days). Secondary prophylaxis was stopped in 13 of the 14 patients: the reasons were IFI relapse in five patients (36%), undifferentiated fever in five patients (36%), acute renal injury in two patients (15%), and a severe electrolyte abnormality in one patient (8%). According to the RIFLE criteria, four patients had acute kidney injury, and one patient was at risk for renal dysfunction.

Five patients (36%) had breakthrough IFIs (patients 1, 3, 5, 7, and 13 in Table 1). Patient 1 had a history of allogeneic stem cell transplantation complicated by graft-versus-host disease and received chronic immunosuppressive therapy with corticosteroids. He had a partial response to his initial treatment of invasive aspergillosis and mucormycosis but had a relapse after 6 weeks of secondary prophylaxis and also experienced acute renal injury. Patient 3 had a relapse while receiving salvage chemotherapy with clofarabine and cytarabine 18 days after complete response of his IFI to the initial treatment; he was severely neutropenic for 4 months. Patient 5 had progression of acute myeloid leukemia while receiving secondary prophylaxis. He then received salvage chemotherapy with high-dose daunorubicin and had intermittent neutropenia for about 3 months. His chemotherapy course was complicated by bacterial infections and disseminated cytomegalovirus. His prophylaxis was stopped at 26 days because of possible IFI affecting the lungs. Patient 7 had an initial partial response of sinus mucormycosis to L-AmB at 9 months of treatment. He had an infection relapse after receiving L-AmB weekly for 128 days; his antifungal course was complicated by relapsed leukemia involving the central nervous system requiring salvage chemotherapy with hyper-CVAD and imatinib (Gleevec). He also had acute renal injury. Patient 13 experienced breakthrough invasive candidiasis after 29 days of secondary prophylaxis while receiving salvage chemotherapy with idarubicin and cytarabine. He was neutropenic for 1 week.

Eleven patients died. The cause of death was attributed to relapsed IFI in 1 patient and cancer progression in 10 patients. No autopsies were performed in any of these cases.

Discussion

To our knowledge, this is the first series of cases of IFI in which the efficacy and safety of weekly secondary prophylaxis with L-AmB in preventing infection relapse in a contemporary consecutive cohort of unselected patients with hematological malignancies is

evaluated. We found that weekly L-AmB use was associated with an IFI relapse rate of at least 1/3 of patients. Five patients (36%) had adverse effects of L-AmB; all five had acute kidney injury, and one also had a severe electrolyte abnormality.

The literature contains a paucity of data about secondary prophylaxis in patients with hematological malignancies having histories of IFIs. We identified 13 studies of such patients (Table 2) [4, 17–28]. However, all of these studies suffered from uncontrolled nature and small patient populations and therefore lacked the statistical power for detecting risk factors for IFI relapse. In addition, these studies included heterogeneous populations of patients who had different responses to treatment of initial IFI and various IFI classifications. All studies but one [28] were retrospective. Importantly, none of the studies defined secondary prophylaxis; therefore, we suspect overlap of prophylaxis and ongoing treatment in at least some of the cases. Finally, none of the studies attempted to differentiate between relapse of IFI from reinfection. Therefore, one should interpret these data with caution because of these numerous deficiencies.

Eight reported studies have included patients who received L-AmB daily for secondary prophylaxis [17–24]. In two case reports, three patients undergoing stem cell transplantation received L-AmB at 1 mg/kg/day and had no infection relapses [17, 20]. Authors also reported on a patient who received L-AmB (unknown dose) who did not have a breakthrough IFI [18]. In a case series of 24 patients who received secondary antifungal prophylaxis, 3 patients (13%) had breakthrough IFIs; however, the specific antifungals these patients received were not documented [19]. Also, in a retrospective study of 43 patients who underwent stem cell transplantation, the subjects received L-AmB (0.6–6.5 mg/kg/day) as secondary prophylaxis for 2–54 days [22]. Physicians initiated this prophylaxis after the onset of fever or pulmonary infiltrates, resulting in overlapping treatment and prophylaxis. The authors did not report the number of patients who had relapses but did calculate the IFI-related mortality rate (28%). One case series of six patients who underwent prior surgical resection of IFIs demonstrated no infection relapses after stem cell transplantation in five patients who received daily L-AmB as secondary prophylaxis [24]. A minority of these studies mentioned the use of adjunct surgery, making assessment of individual interventions difficult. Only one published prospective survey included patients who received L-AmB as secondary prophylaxis for IFIs, but was focused on risk factors for breakthrough IFI and did not mention how many patients had infection relapses [26].

Our study had several limitations in view of its retrospective, single–institution nature. The limited number of patients studied and the fact that this stategy was implemented for various reasons at the discretion of the treating physician, precluded the identification of risk factors for relapse of IFI [3] or L-AmB-associated renal toxicity. Finally, in the absence of molecular investigations [3], one could not differentiate with certainty relapse of IFI versus re-infection in some of these patients.

Based on our own results and review of the literature, we did not find strong evidence supporting the use of L-AmB as secondary prophylaxis in patients with hematological malignancies having histories of IFIs. Large well-designed prospective studies validating our experience in such patient populations are needed. An ideal registry should separate patients undergoing stem cell transplantation from those receiving cytotoxic chemotherapy and include specific definitions of secondary prophylaxis, IFI reinfection, IFI relapse, and complete and partial response to IFI treatment and a careful assessment of risk factors associated with IFI relapse.

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Table 1

Characteristics of patients with previous IFIs who received weekly L-AmB as secondary prophylaxis at MD Anderson (2003–2009)

			Prior IFI				Secondary prophylaxis		Second IFI				
Patient	**Underlying disease status[1]**	**Age (years) /sex**	**Organ involved**	**Pathogen**	**Diagnostic certainty[2]**	**Treatment (duration)[3]**	**Dose (mg/kg/weight)**	**Duration (days)**	**Organ involved**	**Pathogen**	**Diagnostic certainty[2]**	**L-AmB–attributable side effect**	**Follow-up**
1	MCL, complete remission	55/M	Lungs	*Aspergillus niger, Rhizopus*	Proven	L-AmB + Vori (6 weeks)	6.5	59	Lungs, sinus	*Aspergillus* species	Probable	Acute renal injury	Death because of IFI at 1 month
2	AML, complete remission	52/M	Lungs	*Aspergillus glaucus*	Probable	L-AmB + ANF (4 weeks)	5	16	Lungs	Aspergillus spp	-	Acute renal injury	Alive after 1 year
3	AML, refractory	44/M	Lungs	unknown	Possible	Caspo + Vori (6 weeks)	10	18	Lungs	unknown	Possible	no	Death because of AML at 1 year
4	CML, refractory	51/M	Lungs	unknown	Possible	L-AmB (2 weeks)	6.2	27	-	-	-	Acute renal injury	Death because of CML at 3 months
5	AML, refractory	55/M	Lungs	unknown	Possible	L-AmB + Caspo (4 weeks)	7.5	26	Lungs	unknown	Possible	no	Death because of AML at 3 months
6	AML, complete remission	60/F	Foot Lungs	*Fusarium* species	Proven	L-AmB + Caspo (5 weeks)	7.5	20	-	-	-	no	Alive after 3 months
7	ALL, relapsed	27/F	Sinus	*Rhizopus*	Proven	L-AmB + Vori (9 months)	5	128	Sinus	*Candida krusei*, *Candida glabrata*	Probable	Acute renal injury	Death because of ALL at 1 year
8	ALL, complete remission	72/F	Lungs	*Aspergillus* species	Proven	L-AmB + Caspo (7 weeks)	7.5	70	-	-	-	no	Death because of ALL at 3 years
9	ALL, complete remission	70/M	Lungs	*Aspergillus fumigatus*	Probable	L-AmB + Caspo (4 weeks)	5	42	-	-	-	no	Death because of ALL at 1 year
10	ALL, complete remission	49/M	Lungs Sinus	unknown	Possible	L-AmB + Caspo (4 weeks)	7.5	96	-	-	-	no	Alive at 3 years
11	BPL, relapsed	56/M	Lungs Skin	*Mucor circineloides*	Proven	L-AmB + Caspo (4 months)	5	49	-	-	-	no	Death because of ALL at 2 months
12	AML, relapsed	73/M	Lungs	unknown	Possible	L-AmB + Posa (5 weeks)	9	14	-	-	-	yes	Death because of AML at 5 months
13	AML, relapsed	57/F	Blood Skin	*Candida tropicalis*	Proven	Caspo + Vori (2 weeks)	9	29	Lungs Skin	*Candida tropicalis*	Proven	no	Death because of AML at 1 year
14	AML, complete remission	52/F	Mandible	*Rhizopus*	Proven	L-AmB (10 weeks)	5	14	-	-	-	Acute renal injury	Death because of AML at 3 years

[1] MCL, mantle cell lymphoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia; BPL, biphenotypic leukemia.

[2] European Organization for Research and Treatment of Cancer and Infectious Diseases Mycoses Study Group criteria.

[3] Vori, voriconazole; ANF, anidulafungin; Caspo, caspofungin; Posa, posaconazole.

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Table 2

Summary of published reports of studies of patients with hematological malignancies and histories of IFIs who received secondary antifungal prophylaxis and underwent further chemotherapy and/or hematopoietic stem cell transplantation

Reference	Study type	Patient population[1]	Prior IFI[2]	Drug[3]	Treatment duration	Prophylaxis stopped/adverse effects	Breakthrough IFI	Comments
Mele et al. [17]	Case reports	Two patients with AML and PA who received consolidation therapy and chemotherapy, respectively	IA	L-AmB (1 mg/kg/day)	13–16 days	0/2	0/2	L-AmB use discontinued after cell-count recovery
Sevilla et al. [18]	Case series	7 patients with leukemia undergoing peripheral blood SCT	IA	(5) Itra + L-AmB (1) Itra (1) L-AmB	4–22 months 3 months 48 months	0/5 0/1 0/1	0/5 0/1 0/1	Absence of microbiological data in 4 patients
Nosari et al. [19]	Case series	24 patients; 9 underwent SCT (6 allo, 1 MUD and 2 auto), 2 of them underwent prior pulmonary lobectomy and 15 patients with leukemia on continued chemotherapy	IA	(4) Itra (5) L-AmB L-AmB + Itra (3 mg/kg/day) Amp B + Itra (1 mg/kg/day)	ND	ND	3/24	Overlap between treatment and secondary prophylaxis
Tedeshi et al. [20]	Case report	1 patient with AML undergoing 2 courses of consolidation therapy and auto SCT	M	L-AmB (1 mg/kg/day)	14 days	0/1	0/1	
Cordonnier et al. [21]	Case series	11 patients with leukemia undergoing allo SCT (9) or consolidation therapy (2)	IA (10) IC (1)	Vori (400mg/day)	44–245 days	0/11	0/11	
Kruger et al. [22]	Case series	43 patients undergoing SCT (2 auto, 41 peripheral blood SCT)	IA (11) IC (1)	L-AmB (0.6–6.5 mg/kg/day)	2–54 days	0/43	ND	L-AmB was started after the onset of fever or pulmonary infiltrates. IFI related death 28% (12/43)
Vaidya et al. [23]	Case series	27 patients undergoing SCT (15 auto, 12 allo) 9 patients with surgical excision of IFI	IA (19)	(12) Itra (5 mg/kg/day) (12) Amp B (0.5 mg/kg/day) (1) Vori (8 mg/kg/day) (2) Fluco (3 mg/kg/day)	ND	ND	3/27	
Nosari et al. [24]	Case series	6 patients with leukemia had pulmonary surgery for IFI and underwent SCT (3 allo, 3 auto)	IA (4) M (1)	(5) L-AmB (3 mg/kg/day) (1) Vori (400 mg/day)	ND	ND	0/6	
De Fabritis et al. [25]	Retrospective	18 patients with hematological malignancies underwent allo SCT	IA (5) IC (1)	Caspo (50 mg/day)	ND	0/18	2/18	Overlap between continuation of treatment and prophylaxis
Comely et al. [26]	Prospective survey	124 patients with AML, 14.5% had surgical resection of the IFI	ND	(50) Itra (24) Vori (17) Amb B (10) L-AmB (4) Caspo	ND	ND	26/124	Study was focus on risk factors for breakthrough IFI
Zhang et al. [27]	Retrospective	49 patients with ALL (25), AML (10), other (14) who underwent SCT (20 auto, 29 allo)	ND	(23) Vori (20) Itra (3) Caspo (2) Fluco (1) Amp B	15–110 days	0/49	9/49	6.4% IFI-related mortality at 2 years after transplantation. 23 cases with prior possible IFI
Vehreschild et al. [4]	Retrospective	75 patients with AML (61), ALL (10), lymphoma (3) and BPL (1) undergoing chemotherapy or SCT (20 allo, 4 auto)	IA (11) IC (2)	(28) Caspo (50–70 mg/kg/day) (47) Itra (400–600 mg/kg/day)	ND	2/75	9/28 15/47	Despite antifungal prophylaxis, risk of breakthrough IFI was high in both groups
Cordonnier et al. [28]	Prospective Open Label	45 patients (41 acute leukemia)	IA (31) IC (5)	Vori (400 mg/kg/day)	5–180 days	3/45	2/45	

[1] AML, acute myeloid leukemia; PA, primary amyloidosis; SCT, stem cell transplantation; allo, allogeneic; auto, autologous; MUD, matched unrelated donor; ALL, acute lymphocytic leukemia; BPL, biphenotypic leukemia.

[2] IA, invasive aspergillosis; IC, invasive candidiasis; M, mucormycosis; ND, no data.

[3] Itra, itraconazole; Vori, voriconazole; Fluco, fluconazole; Caspo, caspofungin.