original research report

Once-weekly liposomal amphotericin B for prophylaxis of invasive fungal infection after graft-versus-host disease in allogeneic hematopoietic stem cell transplantation: a comparative retrospective single-center study

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BACKGROUND AND OBJECTIVES: The liposomal formulation of amphotericin B (LAmB) has been shown to cause few and mild infusion-related reactions, while achieving high plasma and tissue concentrations compared with conventional amphotericin B. We investigated the efficacy and safety of high-dose LAmB (7.5 mg/kg once weekly) prophylaxis of fungal infections in allogeneic stem-cell transplanted (allo-SCT) patients with graft-versus-host disease (GvHD).

DESIGN AND SETTING: Retrospective, comparative, single-center.

METHODS: Forty-two patients receiving high-dose prednisone for GvHD after allo-SCT had LAmB prophylaxis; 83 patients in the control group received other antifungal prophylaxis.

RESULTS: In the LAmB prophylaxis group, the median duration of treatment was 7 weeks. The cumulative incidence of invasive fungal infection was 8% at 1 year after transplantation, 8% at 2 years and 16% at 3 years in the LAmB group vs. 36% at 1 year, 44% at 2 years and 49% at 3 years in the other prophylaxis group (*P*=.008). Fungal infection-related mortality after transplantation was observed in none of the patients in the LAmB prophylaxis group vs. 12 patients (14%) at 1 year, 14 patients (17%) at 2 years and 16 patients (19%) at 3 years in the control group (*P*=.005). The tolerance of the treatment was good with only 5 patients (12%) having a reversible nephrotoxicity leading to temporary treatment discontinuation.

CONCLUSIONS: High-dose LAmB prophylaxis seems effective and well tolerated in this short series of allo-SCT patients with GvHD. Prospective clinical studies are required to confirm these results.

Invasive fungal infections (IFI) cause significant morbidity and mortality in patients undergoing hematopoietic stem-cell transplantation (HSCT) who have prolonged neutropenia or a severe graft-versus-host disease (GvHD) treated with high-dose corticosteroids and long-term immunosuppressive therapy.[1,2] The use of steroids for GvHD treatment represents a major risk factor for long-term infections, with invasive aspergillosis (IA) as the principal cause of infectious-related mortality.[3,4] This suggests that efforts are warranted to develop optimal antifungal preventive strategies after reduced-intensity conditioning allogeneic stem-cell transplantation (allo-SCT).[5,6] We and others have previously shown that the use of high doses of corticosteroids for GvHD treatment represent a major risk factor for long-term infections, with IA being the principal cause of infectious-related mortality.[3,4] The widespread use of prophylactic oral triazoles has limitations related to poor absorption, inter-individual variability in metabolism and hepatic toxicity.[7-9] Oral triazoles are evaluated in this setting and voriconazole was evidenced recently to be more effective than fluconazole/itraconazole in preventing IFI in patients receiving corticosteroids for GvHD.[10,11]

For a long time, amphotericin B (AmB) deoxycholate has been the best choice for antifungal prophylaxis due to its broad antifungal spectrum and minimal risk of resistance development. However, we used AmB deoxycholate for many years, and it was associated with significant infusion-related toxicity and long-term severe nephrotoxicity, which is a major limitation in allo-SCT patients already receiving nephrotoxic drugs such as cyclosporin A.[12,13]

The liposomal formulation of amphotericin B (LAmB) has been shown to cause few and mild infusion-related reactions,[14-18] while achieving high plasma and tissue concentrations compared with conventional amphotericin B.[15-17] The introduction of LAmB in the transplantation setting has increased the rate of therapeutic success of mycological infections with a good safety profile.[19]

In two placebo-controlled prophylactic trials, LAmB was effective for preventing fungal colonization and invasive fungal infections, respectively, in allo-SCT and liver transplantation.[20] Moreover, recent studies have suggested that a once weekly high-dose of LAmB could be well tolerated as prophylactic antifungal treatment in immunocompromized patients.[21,22] In the present retrospective study, transplant patients with GvHD receiving a weekly high dose of LAmB for antifungal prophylaxis were compared to control patients receiving other antifungal prophylaxis with regards to efficacy and safety.

Table 1. Characteristics of the patients and transplantations.

Characteristics	LAmB prophylaxis group	Other prophylaxis group
Number of patients	42	83
Male/female	14/28	33/50
Age in years, median (range)	51 (18-70)	49 (18-66)
Diagnosis		
Acute myeloid leukemia	10 (24)	25 (30)
Myelodysplastic syndrome	0	5
Acute lymphoblastic leukemia	4 (10)	8 (10)
Chronic myeloid leukaemia	2	2
Myeloproliferative disease	3	1
Non-Hodgkin lymphoma	9 (21)	12 (14)
Hodgkin lymphoma	0	4
Chronic lymphocytic leukemia	5 (12)	2 (2)
Multiple myeloma	5 (12)	14 (17)
Metastatic solid tumors	4 (10)	10 (12)
Graft source		
Bone marrow	2 (5)	10 (12)
Peripheral blood stem cells	34 (81)	64 (77)
Umbilical cord blood	6 (14)	8 (10)
Bone marrow + peripheral blood stem cells	0	1 (1)
Allogeneic stem cell transplantation		
Matched unrelated donor/umbilical cord blood	6/6 (29)	10/8 (22)
Sibling	30 (71)	65 (78)
Conditioning regimen		
Standard	2 (5)	5 (6)
Reduced intensity conditioning	40 (95)	78 (94)
Flu-Bu-ATG	22	36
Flu-TBI	7	10
Flu-Bu-TLI	1	16
Others	10	16

Values are number (%) unless otherwise noted. Flu, fludarabine; Bu, busulfan; ATG, antithymocyte globulin; TBI, total body irradiation 2 Gy; TLI, total lymphoid irradiation.

PATIENTS AND METHODS

This was a retrospective study performed at the Paoli-Calmettes Institute Cancer Centre, Unit of Transplantation and Cellular Therapy, Marseille, France. Patients who received high-dose prednisone (2 mg/kg/day) for acute and/or chronic GvHD therapy after allo-SCT from 1 January 2003 to 31 December 2007 were identified retrospectively. The weekly dose of 7.5 mg/kg was chosen because of the nonlinear pharmacokinetics of LAmB at higher doses, and the fact that this dose is below the maximally tolerated dosage of LAmB.[14] Most often, LAmB was administered on an outpatient basis. Patients were eligible for this prophylaxis schedule if they underwent allo-SCT, and were receiving first-line active corticosteroid therapy (2 mg/kg/day) for acute GvHD. LAmB infusions were started within 24-48h after the beginning of corticosteroid therapy. Patients had no previous history, evidence or suspicion of an invasive mycosis due to a filamentous fungus (ruled out by standard procedures),[26] and had not received any other concomitant antifungal prophylaxis. Also, patients were not treated with LAmB if (i) there was clinical and laboratory evidence of veno-occlusive disease, (ii) serum creatinine was >1.5 times the upper limit of normal for age, (iii) hypokalemia was <3.0 mEq/L, and (iv) they had a history of anaphylaxis attributed to LAmB.[22] This treatment was approved by the insti-

tutional review board and patients gave informed consent for analysis of their clinical data. Standard 2008 definitions for possible, probable and proven IFI were used.[23]

Supportive care was identical during the whole study period. Pneumocystis pneumonia prophylaxis consisted of trimethoprim-sulfamethoxazole (10 mg/kg/day trimethoprim) administered at pre-transplantation and when the neutrophil count exceeded 500/µL twice weekly. As soon as the neutrophil count exceeded 500/µL, patients received daily oral amoxicillin prophylaxis (500 mg × 3/day) against encapsulated bacteria. Antibacterial prophylaxis was discontinued at the time of systemic immunosuppressive therapy discontinuation. Prophylaxis against herpes simplex virus included intravenous acyclovir (250 mg × 3/day) or oral valacyclovir (500 mg × 2/day) during the first month after allo-SCT. Patients received fluconazole according to the attending physician decision as part of our routine practice. Fluconazole (400 mg/day) was given to patients without a history of IA, from the start of conditioning regimen until day 90 after transplantation.

Empiric broad-spectrum antibiotics were begun for temperature greater than 38.5°C or clinical signs of infection. Patients did not receive systematic or specific oral digestive decontamination.[5]

A lyophilized preparation of LAmB (AmBisome, Gilead Sciences, Paris, France) was reconstituted according to the manufacturer's instructions to give a 2 mg/mL solution. Drug dilutions for injection were prepared as needed with 5% dextrose. All patients received once-weekly intravenous LAmB prophylaxis at a dose of 7.5 mg/kg as a 2 hour-infusion. Toxicity was evaluated using the NCI-CTC score (National Cancer Institute Common Toxicity Criteria).

The primary end-point of the study was the incidence of IFI; secondary endpoints included fungal-related mortality, transplant-related mortality, overall survival and safety. All patients who received antifungal prophylaxis were included in the efficacy and safety analyses. The Kaplan-Meier method was used to estimate the end-points at different times of follow-up and the Gray test (cumulative incidence of IFI, fungal-related mortality, transplant-related mortality) or the log-rank test (overall survival) were used to compare the differences between the LAmB prophylaxis group and the control group. The numbers of infections in the two treatment groups were compared by the Fisher exact test.

Table 2. Transplantation outcome.

Characteristics	LAmB prophylaxis group n (%)	Other prophylaxis Group n (%)
Acute GvHD (*P*=.03617)	33 (79)	48 (58)
Grade 2 (*P*=.5992)	19 (45)	32 (39)
Grade 3-4 (*P*=.1294)	14 (33)	16 (19)
Chronic GvHD		
Limited	6 (14)	15 (18)
Extensive	28 (67)	51 (61)
Fungal prophylaxis		
LAmB	42 (100)	0
Fluconazole	NA	59 (71)
Voriconazole	NA	6 (7)
Itraconazole	NA	5 (6)
Caspofungine	NA	4 (5)
Posaconazole	NA	2 (2)
Not available	NA	7 (8)

GvHD: graft-versus-host disease

Table 3. Invasive fungal infection outcomes at the last follow up after transplantation.

IFI	LAmB prophylaxis group (n=42) (%)	Other prophylaxis group (n=83) (%)
Possible	2 (5)	22 (27)
Probable	4 (10)	11 (13)
Proven	0	2 (2)
Total	6 (14)	35 (42)

RESULTS

Of 125 patients presenting with GvHD and treated with corticosteroids, the LAmB prophylaxis group included 42 patients (acute GvHD, 33 patients; chronic GvHD, 34 patients) who had received once-weekly high-dose LAmB (7.5 mg/kg) prophylaxis. The control group was composed of 83 patients (acute GvHD, 48 patients; chronic GvHD, 66 patients) who had received other systemic prophylaxis; some patients had both acute and chronic GvHD. Except for acute GvHD, both groups were comparable (*P*=NS) as for age, disease characteristics, graft source, donor type, and the conditioning regimen intensity (**Table 1**). Acute GvHD was more frequent in the LAmB

Table 4. Outcome at the last follow up after transplantation.

Outcome	L-AmB prophylaxis group (n = 42)	Other prophylaxis group (n = 83)	*P*
Overall Survival			
At 1 year	67%	58%	.256
At 2 years	55%	42%	
Causes of death, n (%)			
Underlying hematological disease	9 (21%)	16 (19%)	NS
Infection	1 (2%)	10 (12%)	.3370
GvHD	2 (5%)	3 (4%)	1
Infection plus GvHD	2 (5%)	5 (6%)	NS
Multi-organ failure	3 (7%)	1 (1%)	NS
Transplant-related mortality			
At 1 year	13%	15%	.671
At 2 years	25%	29%	
Fungal-related mortality			
At 1 year	0	14%	.005
At 2 years	0	17%	

Values are number (%) unless otherwise noted. NS=Not statistically significant.

Table 5. Cause of death by infection at the last follow up after transplantation.

Cause of death by infection	L-AmB prophylaxis group (n=42)	Other prophylaxis group (n=83)
Total	**3 (7%)**	**15 (18%)**
Infection alone	**1 (2%)**	**10 (12%)**
Viral (CMV)	1	2
Bacterial (*Staphylococcus aureus*)	0	1
IFI Proven	0	1
IFI Probable	0	2
IFI Possible	0	4
Infection plus GvHD	**2 (5%)**	**5 (6%)**
Viral (CMV)	2	1
Bacterial (*Enterobacter*)	0	1
IFI Proven	0	0
IFI Probable	0	0
IFI Possible	0	3

group (33/42; 79%) as compared to the control group (48/83; 58%) (*P*=.03617). Other relevant early transplant-related events are summarized in **Table 2**. The median dose of LAmB prophylaxis was 500 mg/week (range 300-650 mg/week) for a median duration of 7 weeks of treatment (range 2-15 weeks).

The global incidence of IFI was 14% (6 patients) in the LAmB group vs. 42% (35 patients) in the control group (*P*=.002). According to diagnostic criteria and revised definitions of invasive fungal disease of EORTC/MSG consensus group, 23 in LAmB group, 2 patients had possible IFI and 4 patients had probable IFI vs, in control group, 22 patients with possible IFI and 11 patients with probable IFI. Only 2 patients had proven IFI, both in the control group (**Table 3**).

The outcomes in the two groups at the last follow up are summarized in **Table 4**.The cumulative incidence of IFI was 8% at 1 year after transplantation, 8% at 2 years and 16% at 3 years in the LAmB group vs. 36% at 1 year, 44% at 2 years and 49% at 3 years in the control group (*P*=.008) (**Figure 1**). The cause of death by infection, alone or with GvHD, in two groups at the last follow up is summarized in **Table 5**. No fungal infection-related mortality after transplantation was observed in LAmB group vs. 12 deaths (14%) related to fungal infection at 1 year, 14 deaths (17%) at 2 years and 16 deaths (19%) at 3 years in the control group (*P*=.005) (**Figure 1**). There was no difference between the transplant-related mortality rates in the two groups: 18% from 1 year through 3 years after transplantation in the LAmB group vs. 16% at 1 year, 19% at 2 years and 21% at 3 years in the control group (*P*=.99)(**Figure 2**).There was no difference between the overall survival rates in the two groups: 69% at one year after transplantation, 55% at 2 years and 55% at 3 years in the LAmB group vs. 75% at one year, 64% at 2 years and 58% at 3 years in the control group (*P*=.60)(**Figure 2**).

The tolerance of the treatment was good. Toxicity was observed in only 5 patients (12%) who had nephrotoxicity, which led to temporary treatment discontinuation but was reversible. All patients were taking concomitantly cyclosporin A or other nephrotoxic drugs such as ganciclovir, amikacin or vancomycin.

DISCUSSION

This study evaluated the efficacy and safety of once-weekly prophylactic administration of high-dose (7.5 mg/kg) LAmB in adult patients treated in our institution, receiving high-dose corticosteroids for acute or chronic GvHD therapy after allo-SCT.

One report suggested that antifungal prophylaxis

with low-dose LAmB is feasible and effective in patients undergoing intensive chemotherapy.[24] Another study showed that a once-weekly 15 mg/kg LAmB dose given to adult patients undergoing allo-SCT achieved high, sustained tissue concentrations, similar to those achieved with conventional (1 mg/kg) daily dosing (Gubbins et al., abstract at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004).

The schedule of a single dose 7.5 mg/kg once weekly was chosen because of the nonlinear pharmacokinetics of LAmB at higher doses, as well as because this dose is below the maximumly tolerated dose of LAmB.[14] However, one challenging aspect of our study was the need for weekly intravenous administration of LAmB as compared to oral administration with new triazoles such as voriconazole or posaconazole. Alternative prophylactic therapy with an echinocandin (ex, caspofungin) requires daily intravenous administration.

If ambulatory weekly high-dose LAmB proved to be tolerable, this would provide an acceptable prophylactic regimen which could be administered for long periods, further improving the safety and outcome of RIC or myeloablative allo-SCT. Moreover LAmB has a broad spectrum of action against molds and yeasts including Candida spp., Aspergillus spp. and filamentous fungi such as zygomycetes and could thus offer larger antifungal prophylaxis.[25]

The incidence of IFI and fungal infection-related mortality were significantly reduced in the LAmB prophylaxis group compared to the control group. However, we did not observe any difference in overall survival and in transplant-related mortality between the two groups. This could be due to the higher frequency of acute GvHD in the LAmB prophylaxis group compared to the control group.

In contrast with reports of concerns about a high rate of hypokalemia, our data indicate that LAmB can be given safely at high doses.[14] Toxicity was observed in 5 patients (12%) who had a reversible nephrotoxicity which led to temporary treatment discontinuation. All patients were taking concomitantly nephrotoxic drugs.

This study has the limitations inherent to a retrospective analysis of a non-randomized study. Moreover the incidence of IFI in the control group could appear high (36% after one year). We cannot exclude that IFI was overdiagnosed, particularly for possible IFI. It should be kept in mind that these patients were at high risk of fungal infections: they were not only allo-SCT patients, but they had also severe GvHD and therefore received high-dose corticotherapy. The infection-related mortality, which is independent of the initial diagnosis, was clearly lower for the group with LAmB prophylaxis (0% vs. 14% for the control group after one year).

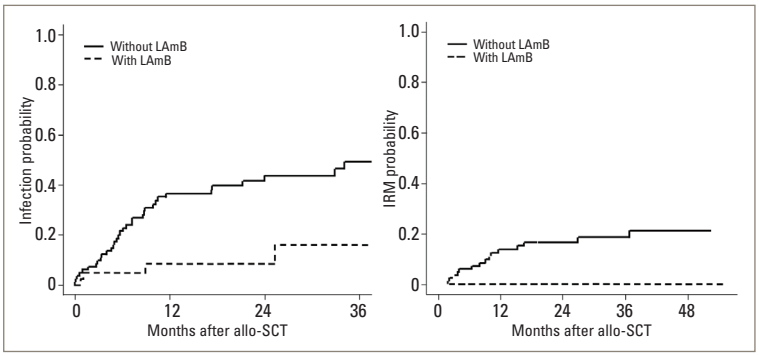

Figure 1. Cumulative incidence of invasive fungal infections and fungal infection-related mortality according to antifungal prophylaxis.

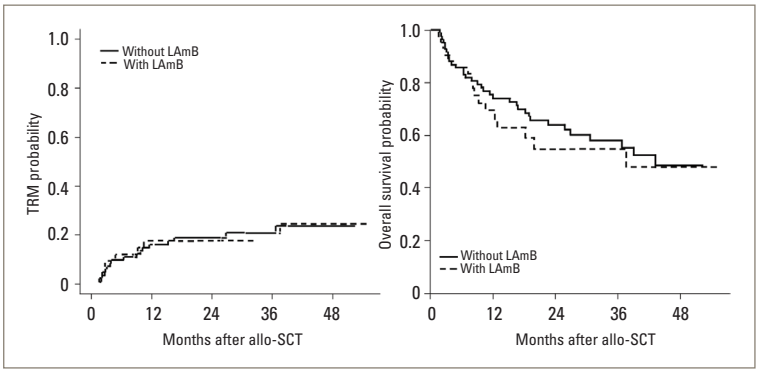

Figure 2. Overall survival and transplant-related mortality (TRM) according to antifungal prophylaxis.

We present the patient outcomes with a follow-up of 3 years after transplantation even though these data are most probably well beyond the pharmacological effect expected for a median 7-week treatment. Nevertheless we estimate that this long-term follow-up is important evidence that the choice of prophylaxis is associated with durable and different outcomes. Despite the limitations of this study and the short series of patients, LAmB prophylaxis of IFI seems effective and well tolerated reducing both the incidence of IFI and the fungal infection-related mortality in allo-SCT patients presenting as severe GvHD. Further prospective clinical studies are required to confirm these single-center data.

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Author contributions

Jean El-Cheikh collected and analyzed data, performed statistical analysis, provided clinical care, wrote and revised the manuscript; Luca Castagna and Ling Wang collected data provided clinical care and commented on the manuscript; Catherine Faucher, Sabine Fürst, and Mohamad Mohty; recruited patients, provided clinical care and commented on the manuscript; Benjamin Esterni, performed statistical analysis; Pierre Berger and Stephane Ranque provided microbiological control, and commented on the manuscript; Didier Blaise recruited patients, provided clinical care and commented on the manuscript.

Conflict of Interest

None declared

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