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Tolerability and outcome of once weekly liposomal amphotericin B for the prevention of invasive fungal infections in hematopoietic stem cell transplant patients with graft-versus-host disease

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Abstract

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Conflict of Interest Statement
The authors declare that there are no conflicts of interest.

Background—Invasive fungal infections remain problematic in immunosuppressed allogeneic stem cell transplant recipients and the use of corticosteroids for the treatment of graft-versus-host-disease can increase the risk three-fold. Although antifungal prophylaxis has been shown to decrease the incidence of infection, the optimal antifungal prophylactic regimen in this patient population has yet to be identified. Since early diagnosis of fungal infections might not be possible and the treatment of established fungal infections might be difficult and associated with high infection related mortality, prevention has become an important strategy in reducing overall morbidity and mortality. While triazoles are the preferred agents, some patients are unable to tolerate them and an alternative drug is warranted.

Objectives—To assess the tolerability of once weekly liposomal amphotericin B as a prophylactic strategy in patients undergoing stem cell transplantation by evaluating any adverse events leading to its discontinuation. In terms of efficacy, to also compare the outcome and incidence of invasive fungal infections in patients who received amphotericin B, triazoles, and echinocandins.

Results—A total of 101 allogeneic transplant recipients receiving corticosteroids for the treatment of graft-versus-host-disease and antifungal prophylaxis were evaluated from August 2009 to September 2012. Liposomal amphotericin B 3 mg/kg intravenous once weekly was found to be well-tolerated. The incidence of invasive fungal infections was 19%, 17%, and 7% in the liposomal amphotericin B, echinocandin, and triazole groups, respectively. Two deaths occurred in the liposomal amphotericin B group and one death occurred in the echinocandin group. None of the deaths were fungal infection-related.

Conclusion—Antifungal prophylaxis with liposomal amphotericin B was well-tolerated but the incidence of invasive fungal infections in patients receiving liposomal amphotericin B was higher than other antifungal agents in this study. The optimal dose and schedule of liposomal amphotericin B for antifungal prophylaxis in this patient population is still not known and considering its broad spectrum activity, prospective trials in comparison to triazoles are warranted.

Keywords

Liposomal amphotericin B; graft-versus-host-disease; invasive fungal infections; hematopoietic stem cell transplant; corticosteroids; prophylaxis

Introduction

Invasive fungal infections (IFIs) can cause significant morbidity and mortality in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Depending on risk factors, the rate of infection is between 10 and 25%, with fatalities between 35 to 50% for invasive candidiasis and 65 to 90% for invasive aspergillosis.[1,2] There are many well-known risk factors for the development of infection in this patient population. The use of corticosteroids for the treatment of graft-versus-host disease (GvHD) increases this risk three-fold.[1,3–5] To reduce the morbidity and mortality associated with this complication, several prophylactic antifungal regimens have been used and studied including triazoles, echinocandins, and amphotericin B. While triazoles are available orally and have the most evidence to support its role as prophylaxis, barriers such as hepatic dysfunction, drug interactions, and the ability to obtain therapy can limit their use.[6] Furthermore, triazole-based prophylaxis may result in

an increase in invasive aspergillosis compared to invasive candidiasis.[4] Although echinocandins have been shown to be effective in preventing IFIs, there is still a need for effective broad spectrum antifungal prophylaxis as the incidence of breakthrough infections were still high with echinocandins.[7]

Amphotericin B (AmB) is a polyene antifungal with a wide spectrum of activity against yeasts and molds.[3,4,8] It binds to sterols on the cytoplasmic membrane to increase permeability, resulting in leakage of molecules leading to cell death. Resistance is rare but can occur through mutations in the ergosterol synthesis pathway. For many years, AmB has been the gold standard for the treatment of IFIs. However, the use of AmB often produces nephrotoxicity and infusion-related adverse effects, limiting its administration. Reduced toxicity has been observed with newer lipid formulations. Liposomal amphotericin B (LAmB) is a unilamellar formulation of AmB that allows for the delivery of higher doses with decreased toxicity.[9] LAmB, compared to AmB, has a longer half-life (174 hours versus 48 hours) which allows for less frequent dosing.[8,9] In addition, its intravenous formulation makes it an attractive option in patients unable to tolerate oral medications.

To our knowledge, there is no literature to support an optimal dosing regimen for LAmB as a prophylactic agent in the setting of HSCT. Several studies evaluating different amphotericin B formulations for fungal prophylaxis have yielded conflicting results, likely due to the differences in study design, patient population, and dosing regimen.[10–14] Specifically, few studies have evaluated LAmB or compared it to triazoles or echinocandins for fungal prophylaxis in HSCT patients receiving steroids for the treatment of GvHD. Chaftari *et al*. prospectively compared amphotericin B lipid complex (ABLC) 7.5 mg/kg intravenous once weekly as an alternative to posaconazole for prophylaxis in HSCT patients.[15] Although there were no differences in the incidence of IFIs between the ABLC versus posaconazole group (5% versus 0%, p=0.48), the use of ABLC for fungal prophylaxis in HSCT patients could not be recommended due to a significantly higher rate of nephrotoxicity. A different outcome was observed when Cheikh *et al*. performed a single center, retrospective comparison of LAmB 7.5 mg/kg intravenous once weekly to various azoles and caspofungin for fungal prophylaxis in allogeneic HSCT patients being treated with high dose steroids for GvHD.[16] Investigators found that LAmB, compared to the other prophylaxis group, significantly decreased IFIs (8% at 1 year versus 36% at 1 year, p=0.008) and fungal related mortality (0% at 1 year versus 14% at 1 year, p=0.005). It was concluded that LAmB was effective and well tolerated in this patient population. It has been reported that LAmB is associated with fewer infusion-related reactions and less nephrotoxicity which could explain the different outcomes in these two studies.[5] Given the results presented, the role and dose of amphotericin B for fungal prophylaxis in HSCT patients still remains unclear.

Prior to available published data supporting LAmB 7.5 mg/kg intravenous once weekly, our institution has been using LAmB 3 mg/kg intravenous once weekly since 2008 as an alternative for antifungal prophylaxis in patients who are unable to tolerate or receive triazoles or echinocandins and were being treated for GvHD with corticosteroids (prednisone ≥ 20 mg daily or equivalent). All of the patients were dosed using their actual body weight. The purpose of this study was to determine the tolerability of LAmB as

antifungal prophylaxis in HSCT patients and to compare the outcome of LAmB 3 mg/kg intravenous once weekly to mold-active triazoles and echinocandins for the prevention of IFIs in HSCT patients receiving corticosteroids (prednisone ≥ 20 mg daily or equivalent) for the treatment of GvHD.

Patients and methods

Study design and patients are included in Figure 1. A single center comparative chart review was performed at our institution. Patients treated with steroids (prednisone ≥ 20 mg daily or equivalent) for acute or chronic GvHD after allogeneic stem cell transplantation during the time period August 2009 to September 2012 were retrospectively identified. Patients were then grouped according to the fungal prophylactic therapy they received. Those who previously received a triazole but were switched to an echinocandin or LAmB were included in the arm of the agent they were switched to. This study was approved by the institutional review board.

Allogeneic stem cell transplant recipients were included in the study if they received single agent fungal prophylaxis at the time of GvHD treatment. Patients who received at least one dose of LAmB or one week of echinocandin and triazole prophylaxis were eligible for study inclusion. Patients with a prior history of IFIs were also included in the study. Patients were excluded if they were treated for a fungal infection in the previous 28 days. Patients were followed until discontinuation of prophylaxis or until proven or presumed fungal infection requiring treatment. Rates of IFIs were compared in each arm. Other baseline information collected included transplant conditioning regimen, duration of neutropenia, use of immunosuppressive agents such as alemtuzumab and fludarabine, GvHD prophylaxis regimen, cytomegalovirus (CMV) serostatus, dose and duration of steroid, and indications for not using a triazole for prophylaxis.

Data analysis

The primary end point of this study was to assess the tolerability of LAmB. All patients who received one dose of LAmB were included in the analysis. Any adverse events that led to the discontinuation of LAmB were evaluated. The secondary objectives were to compare the incidence of IFIs in each arm. Patients who received at least one week of antifungal prophylactic therapy were assessed. In addition to descriptive statistics, Fisher’s exact test was used to compare the differences between all groups in baseline characteristics and incidence of IFIs. Analysis of variance (ANOVA) was used to compare duration of antifungal prophylaxis.

Definitions

Outcomes were assessed by incidence of IFIs requiring treatment. IFIs were categorized as proven, probable, and possible as defined by the revised definitions by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC).[17]

Proven IFIs were defined as clinical signs and symptoms and radiologic findings suggestive of infection in the presence of the proper host factors with histopathologic or microbiologic documentation of disease from tissue sample biopsies. Host factors include duration of neutropenia, allogeneic stem cell transplant, prednisone > 0.3 mg/kg/day, and T-cell suppression.

Probable IFIs were defined as clinical signs and symptoms and radiologic findings suggestive of infection in the presence of a mycological criteria such as a positive culture from bronchoalveolar lavage fluid, sputum or brush samples, or the detection of serum galactomannan antigen in patients with appropriate host factors.

Possible IFIs were defined as clinical signs and symptoms and radiologic findings suggestive of infection in the absence of a mycological criteria in patients with appropriate host factors.

Results

Of 101 patients evaluated, the LAmB prophylaxis group included 16 patients who received LAmB 3 mg/kg intravenous once weekly. The echinocandin group included 12 patients (caspofungin, 10 patients; micafungin, 2 patients) and the triazole group included 73 patients (voriconazole, 30 patients; posaconazole, 43 patients).

Baseline characteristics of all patients are included in Table 1. All groups were comparable as far as age, underlying malignancy, conditioning regimen intensity, GvHD prophylactic regimen, and CMV serostatus. Additionally, no differences were noted in the incidence or type of GvHD. Four patients in the LAmB group were treated with alemtuzumab post-transplant for GvHD while no patients in the other groups received it. A higher percentage of patients in the echinocandin group experienced prolonged and profound neutropenia and this was statistically different between the three groups. As shown in Table 2, the steroid dose was similar with the majority of patients requiring ≥ 1 mg/kg corticosteroid at initiation of antifungal prophylaxis and the mean days of antifungal prophylaxis were similar in all three groups.

LAmB 3 mg/kg intravenous once weekly was well tolerated; there were no reported adverse events such as nephrotoxicity, infusion reactions, or electrolyte disturbances that led to its discontinuation. Therapy was discontinued in one patient due to an adverse event of back pain which resolved when the infusion was stopped.

As presented in Table 3, the incidence of IFIs was highest in the LAmB group at 19%, followed by the echinocandin group at 17%, and lowest in the triazole group at 5% (p=0.145). There were no proven infections in any of the treatment groups. According to the diagnostic definition of the EORTC consensus group, there were three possible infections in the LAmB group. In the echinocandin group, there was one possible and one probable infection. Both patients received caspofungin. In the triazole group, there were three possible infections and one probable infection.

Although there were four deaths that occurred in patients who were diagnosed with IFIs, none were fungal infection-related. Two of the deaths that occurred in the LAmB group were due to bacterial infections and GvHD. The one death that occurred in the echinocandin group was due to GvHD, Methicillin-resistant *Staphylococcus aureus* pneumonia, and CMV infection. The one death that occurred in the triazole group was due to *Pseudomonas* pneumonia.

The most common reasons for not using a mold-active triazole are presented in Table 4. Hepatic dysfunction was the most common barrier, followed by the patient's inability to pay for therapy. Other reasons included additive potential for QTc interval prolongation, non-compliance, and use of LAmB as secondary prophylaxis following successful treatment response of a previous fungal infection. Although drug interactions with azoles and calcineurin inhibitors are well known, this did not prohibit azole use as our institution has an algorithm in place that incorporates a preemptive dose-reduction strategy of the calcineurin inhibitor, followed by monitoring for adverse effects in addition to twice weekly drug levels. This prevented any event, such as renal or neurotoxicity, that would lead to the discontinuation of the azole or calcineurin inhibitor.

The most common reasons for discontinuation of antifungal prophylaxis are outlined in Table 5. Steroid dose less than prednisone 20 mg daily (or equivalent) was the most common reason, followed by not being able to obtain triazole therapy. In the LAmB group, therapy was discontinued after a patient experienced progression of disease. In the echinocandin group, one patient died of cardiac arrest and one patient pursued hospice care. In the triazole group, two patients pursued hospice and one patient experienced thrombocytopenia and all medications were held. Five patients remained on prophylactic triazole therapy at the conclusion of the study and were not included in this part of the analysis.

Discussion

The prevention of IFIs in immunosuppressed allogeneic stem cell transplant recipients with GvHD remains a challenge as there are many barriers than can limit the use of triazoles. AmB has a broad spectrum of activity against molds and yeasts including *Candida*, *Aspergillus*, and Zygomycetes, offering an advantage over triazoles or echinocandins. Furthermore, lipid-based amphotericin B products have been associated with decreased incidences of nephrotoxicity compared to conventional amphotericin B and is being used at some centers as an alternative antifungal prophylactic agent. This study evaluated the tolerability and outcome of once weekly prophylactic LAmB 3 mg/kg administered intravenously to adult patients receiving corticosteroids for the treatment of GvHD after allogeneic stem cell transplant. To our knowledge, the dose of LAmB 3 mg/kg intravenous once weekly has not been evaluated in published literature and in our study, there were no adverse events leading to discontinuation of therapy compared to a higher dose of LAmB 7.5 mg/kg intravenous once weekly studied by Cheikh *et al*. which reported a 12% incidence of reversible nephrotoxicity leading to temporary treatment discontinuation.[16] Furthermore, our study was consistent with literature supporting liposomal amphotericin B to be less nephrotoxic than the lipid complex formulation where Chaftari *et al*. observed therapy

discontinuation in 53% of patients due to nephrotoxicity at a dose of 7.5 mg/kg intravenous once weekly.[15]

In addition to high dose corticosteroids, prolonged and profound neutropenia can further lead to IFIs regardless of prophylaxis as patients no longer have competent T cells to fight off infection.[3] Our study shows that there was a significant difference between the three groups with more patients in the echinocandin and LAmB group experiencing prolonged and profound neutropenia than the triazole group (42%, 12.5%, and 7%, p=0.005) possibly contributing to higher rates of IFIs. Furthermore, the use of agents such as alemtuzumab or fludarabine can have prolonged and profound lymphocyte depleting effects, thereby increasing the risk for infections. Our study observed a higher incidence of IFIs in the LAmB group that may be explained by the use of alemtuzumab by four patients compared to no patients in the echinocandin and triazole group.

The epidemiology of IFIs has evolved as transplant practices and prophylactic strategies have changed over the last several decades. In our study, the incidence of IFIs in the triazole group was 5% which is consistent with Chaftari *et al.* and other literature reports ranging from 2 to 9% in patients receiving mold-active agents.[12,15,18–21] These findings were not supported by Cheikh *et al*. because the majority of the patients in the azole and echinocandin prophylaxis group (71%) received the non-mold active agent fluconazole. However, the incidence of IFIs in our LAmB group was 19%, which is higher than incidences reported by Chaftari *et al*. and Cheikh *et al*. at 5% and 8%, respectively.[15,16] In spite of this, a statistically significant difference was not detected in our study and it can be argued that LAmB is comparable to triazoles in preventing IFIs in this patient population but larger studies are needed to determine this.

Potential advantages of using LAmB include decreased cost and the convenience of less frequent dosing, as well as a different side effect profile than triazoles. One of the drawbacks of using a triazole in the outpatient setting is the out-of-pocket expense to the patient, which could amount to thousands of dollars a month, possibly leading to non-compliance.[22] In these situations where the patient is unable to pay, an alternative prophylactic agent is needed as the cost of preventing an IFI in these high risk patients outweighs the treatment of it. Furthermore, compared to daily dosing of echinocandins and triazoles, once weekly LAmB may be a convenient intravenous option for patients, decreasing chair time and increasing compliance.

In our study, the mean duration of prophylaxis was comparable to triazoles, and LAmB could be an acceptable prophylactic agent that can be administered for long periods of time to further improve the safety and outcome of allogeneic stem cell transplants. The study is subject to several limitations. The first is the small sample size that made it difficult to detect statistically significant differences. Second, the retrospective analysis made it challenging to capture compliance and all adverse events, especially in patients who received therapy through home health or their local facility. During the study period, the formulary switched from caspofungin to micafungin. Although used interchangeably by some clinicians, micafungin is the only echinocandin approved in the prophylactic setting and this could have resulted in potentially different outcomes in the echinocandin group. Furthermore, the

possibility that IFIs were over-diagnosed cannot be excluded as none of the infections were proven. This situation may arise because this patient population is at very high risk for fungal infections and the threshold for initiating antifungal treatment is low. Additionally, it should be noted that the LAmB group consisted of only possible infections.

Conclusion

Although LAmB 3 mg/kg once weekly is tolerable, larger studies are needed to evaluate its efficacy. The optimal dose and schedule is still not known and considering the broad spectrum activity of LAmB, prospective trials in comparison to triazoles are warranted.

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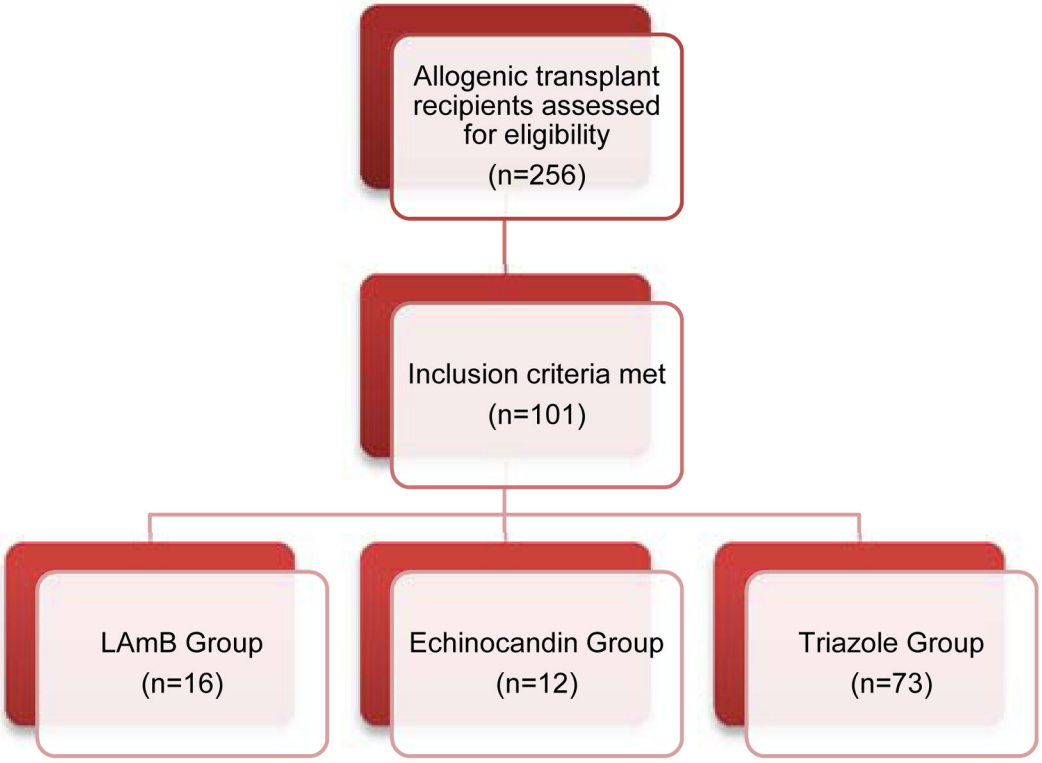

Figure 1.
Study Design and Patients

Table 1

Baseline patient characteristics

	LAmB (n=16)	Echinocandin (n=12)	Triazole (n=73)	P
Age, Years (mean)	45.8	47.5	50	NS
Underlying disease				NS
Acute leukemias/MDS	11 (69%)	10 (83.3%)	46 (63%)	
Chronic leukemias	2 (12.5%)	1 (8.3%)	12 (16.5%)	
Lymphomas	3 (18.5%)	1 (8.3%)	15 (21.5%)	
Conditioning Regimen				NS
Myeloablative	11 69%)	4 (33%)	38 (52%)	
Nonmyeloablative	3 (18.5%)	6 (50%)	18 (25%)	
Reduced intensity	2 (12.5%)	2 (17%)	17 (23%)	
GvHD Prophylaxis Regimen				NS
CSA/MMF	1 (6%)	2 (17%)	5 (7%)	
FK/MMF	2 (12.5%)	3 (25%)	19 (26%)	
FK/MTX	11 (69%)	4 (33%)	36 (49%)	
ATG-based/other	2 (12.5%)	3 (25%)	13 (18%)	
Immunosuppressive Agents[+]				
Alemtuzumab	4 (25%)	0 (0%)	0 (0%)	NS
Prolonged Grade 4 Neutropenia[++]	2 (12.5%)	5 (42%)	5 (7%)	0.005
CMV Status				NS
D+/R+	6 (37.5%)	4 (33%)	19 (26%)	
D+/R−	4 (25%)	4 (33%)	15 (20.5%)	
D−/R−	4 (25%)	2 (17%)	26 (35.5%)	
D−/R+	2 (12.5%)	2 (17%)	13 (18%)	
GvHD				NS
Acute	8 (50%)	7 (58%)	47 (64%)	
Chronic	8 (50%)	5 (42%)	26 (36%)	

MDS=Myelodysplastic syndrome

CSA=Cyclosporine, MMF=Mycophenolate Mofetil, FK=Tacrolimus, MTX=Methotrexate, ATG=Antithymocyte Globulin

D+=Donor Positive, R+=Recipient Positive, R−=Recipient Negative, D−=Donor Negative

NS=Not significant

[+] Post-transplant

[++] Lasting more than 7 days

Table 2

Dose of corticosteroid therapy and duration of antifungal prophylaxis

	LAmB (n=16)	Echinocandin (n=12)	Triazole (n=73)	P
Steroid Dose				
< 1 mg/kg/day	2 (12.5%)	0 (0%)	13 (18%)	
≥1 mg/kg/day	14 (87.5%)	12 (100%)	60 (82%)	
Prophylaxis Days (mean)	59.5	34.5	75	0.125

Table 3

Incidence of invasive fungal infections

	LAmB (n=16)	Echinocandin (n=12)	Triazole (n=73)	P
Proven	0 (0%)	0 (0%)	0 (0%)	
Probable	0 (0%)	2 (17%)	1 (1%)	
Possible	3 (19%)	0 (0%)	3 (4%)	
Total	3 (19%)	2 (17%)	4 (5%)	0.145

Table 4

Barriers to obtaining triazole therapy

	LAmB (n=16)	Echinocandin (n=12)	Triazole (n=73)
Hepatic dysfunction	11	8	N/A
Insurance	2	3	N/A
Drug interactions	1	1	N/A
Other	2	0	N/A

Table 5

Reasons for discontinuation of antifungal prophylaxis

	LAmB (n=16)	Echinocandin (n=12)	Triazole (n=73)
Prednisone < 20 mg daily	7	7	51
Adverse event	1	0	1
Obtained triazole	4	1	N/A
Invasive fungal infection	3	2	4
Organ dysfunction	0	0	9
Other	1	2	3