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Liposomal amphotericin B twice weekly as antifungal prophylaxis in paediatric haematological malignancy patients

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Abstract

Data on antifungal prophylaxis in paediatric cancer patients at high risk for invasive fungal disease (IFD) are scant. Intermittent administration of liposomal amphotericin B (LAMB) has been shown to be safe and effective in adult patients with haematological malignancies. We prospectively evaluated the safety and efficacy of prophylactic LAMB at a dosage of 2.5 mg/kg twice weekly in children at high risk for IFD. Efficacy was compared with that in a historical control group of patients with similar demographic characteristics not receiving LAMB prophylaxis. A total of 46 high-risk patients (24 boys; mean age, 7.7 years) with 187 episodes of antifungal prophylaxis were analysed. The median duration of neutropenia (<500/μL) was 10 days. LAMB was discontinued in four patients because of acute allergic reactions. Median values for creatinine and liver enzymes at end of treatment did not differ significantly from those at baseline. Hypokalaemia (<3.0 mmol/L) occurred with 13.5% of the prophylactic episodes, but was usually mild and always reversible. No proven/probable IFD occurred in patients receiving LAMB prophylaxis. In comparison, five proven and two probable IFDs were observed in 45 historical controls not receiving LAMB prophylaxis (p 0.01). LAMB prophylaxis had no impact on the use of empirical antifungal therapy. Systemic antifungal prophylaxis with LAMB 2.5 mg/kg twice weekly is feasible and safe, and seems to be an effective approach for antifungal prophylaxis in high-risk paediatric cancer patients.

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Introduction

Despite the availability of new antifungal agents, invasive fungal disease (IFD) is still a major cause of morbidity and mortality in paediatric patients undergoing therapy for cancer. In particular, children treated for high-risk acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) or relapsed acute leukaemia are at high risk for IFD and may benefit from systemic prophylactic antifungal measures [1,2]. Whereas posaconazole has been demonstrated to decrease the incidence of IFD in adults undergoing induction therapy for AML or adult haematopoietic stem cell transplant recipients with severe graft-versus-host disease [3,4], the optimal approach to antifungal prophylaxis in paediatric patients is not at all clear, for several reasons. First, several antifungal compounds, including posaconazole, are not approved for children, and a paediatric dosage has not been established for some of them. Second, the use of antifungal triazoles is limited by the potentiation of toxicity when they are co-administered with vinca alkaloids, which constitute a cornerstone in the treatment of acute paediatric leukaemia [5,6]. Moreover, the use of echinocandins (e.g. micafungin, which is approved in children for antifungal prophylaxis) is not feasible

in an outpatient setting, owing to the short half-life of the compounds, necessitating daily intravenous administration.

Liposomal amphotericin B (LAMB) does not have relevant drug–drug interactions, and exhibits lower infusional toxicity and less long-term nephrotoxic side effects than amphotericin B deoxycholate [7]. Owing to the long-half life and substantial tissue penetration of the compound, therapeutic levels of amphotericin B are found in animal tissues for several weeks after treatment [8], and measurable plasma concentrations have been demonstrated for up to 7 days after administration of LAMB at a dosage of 10 mg/kg in paediatric haematopoietic stem cell transplant recipients [9]. We therefore hypothesized that LAMB given twice weekly may be a feasible, safe and effective strategy for antifungal prophylaxis in paediatric cancer patients at high risk for IFD.

Patients and Methods

Study design

From April 2007 through August 2010, all consecutive children treated for high-risk ALL, AML, relapse of ALL or AML, high-risk non-Hodgkin lymphoma (such as B-cell ALL) and severe/very severe aplastic anaemia were included in the analysis, as they were considered to be at high risk for IFD. All patients with prior treatment of proven/probable IFD were excluded from the analysis. Systemic antifungal prophylaxis consisted of LAMB (2.5 mg/kg over 1 h) twice weekly. Topical or inhaled antimycotic compounds were not administered; patients were not admitted to HEPA-filtered rooms, and the use of filtered masks outside the filtered areas was not routinely recommended. The primary endpoint of the study was the evaluation of feasibility of the protocol in terms of safety; secondary endpoints were efficacy and the assessment of drug concentration in a randomly selected subgroup of patients. Written informed consent for antifungal therapy as part of the medically indicated measures of supportive care and for data collection was obtained and documented within the consent procedures for cancer treatment that have been reviewed and approved by the local Ethics Committee.

The historical control group consisted of consecutive patients treated from April 2000 through April 2007 for underlying malignancies comparable to the those of the study group. For the study population and historical controls, chemotherapeutic regimens were either identical (e.g. high-risk ALL or relapsed leukaemia) or were increased in intensity over time (e.g. for subgroups of AML patients). Medical and nursing practices did not differ between the study group and historical controls (e.g. diagnostic testing and nursing practices). None of the historical controls received amphotericin B or an echinocandin as antifungal prophylaxis; however, depending on the comedication, fluconazole or itraconazole was administered in a number of the analysed episodes.

Analysis of amphotericin B concentrations

For assessment of LAMB plasma concentrations, blood was drawn 30 min prior to and after administration of LAMB, immediately centrifuged for 10 min at 1500 ***g***, and stored at −70°C until being assayed. Concentrations of total amphotericin B were measured with a validated HPLC method [10].

Definitions

The duration of an episode of antifungal prophylaxis was defined as the period from day 1 of a cycle of chemotherapy until the day before day 1 of the next cycle of chemotherapy. Because of the continuous administration of chemotherapy during induction therapy for ALL, the duration of an episode of antifungal prophylaxis in these patients was considered to be from the onset of neutropenia until haematopoietic recovery after induction therapy.

Adverse events were analysed according to the NCI Common Terminology Criteria for Adverse Events [11]. For example, allergic reactions of grade I/II consisted of skin reactions, whereas symptomatic bronchospasm requiring parenteral medication and anaphylaxis were graded as grade III and IV adverse events, respectively. Creatinine levels up to 1.5 and >1.5–3 times the upper limit of normal (ULN) were categorized as grade I and II adverse events, respectively, whereas levels >3–6 × ULN and >6 × ULN were categorized as grade III and IV, respectively. Potassium levels less than the lower limit of normal (−3.0 mmol/L) were categorized as grade I hypokalaemia, and levels <3.0–2.5 and <2.5 mmol/L as grade III and IV, respectively. The primary investigators of the study (K.B. and T.L.) rated the adverse events as related or not related to treatment with LAMB, respectively.

IFD was defined as proven, probable and possible according to the revised definitions of the European Organization for Research and Treatment of Cancer/Mycoses Study Group [12]. Neutropenic patients with fever refractory to broad-spectrum antibiotics received empirical antifungal therapy according to standard guidelines [13]. Only patients receiving at least three doses of LAMB were assessed for efficacy. Patients were followed for the occurrence of IFD until 2 months after discontinuation of antifungal prophylaxis.

Statistical analysis

Statistical analysis was performed with BiAS Version 9.02 (Epsilon Publishing). Student's *t*-test was used to compare patients receiving LAMB prophylaxis and historical controls.

TABLE 1. Patient characteristics

	Patients with LAMB prophylaxis		Historical controls	
Number of patients (sex)	44 (24 male, 20 female)		39 (22 male, 17 female)	
Number of cases[a]	46		45	
Age (median (range))	7.7 years (6 months to 21 years)		10 years (3 months to 16 years)	
Underlying diagnosis[a]	HR-ALL	13*	HR-ALL	8**
	ALL relapse	14	ALL relapse	8
	AML	10	AML	18****
	AML relapse	2	AML relapse	4
	NHL	5*	NHL	6
	NHL relapse	1	SAA	1
	SAA	1		
Number of analysed episodes[b]	184		201	
Duration of analysed episode (days) (median (range))	24 (5–104)		28 (4–105)	
Duration of ANC <500/μL (days) (median (range))	10 (0–52)		12 (0–63)	
Duration of ANC <1000/μL (days) (median (range))	15 (3–121)		16 (1–75)	
Number of episodes (%) with prolonged neutropenia (ANC <500/μL for >10 days)	126 (68)		113 (57)	

AML, acute myeloid leukaemia; ANC, absolute neutrophil count; HR-ALL, high-risk acute lymphoblastic leukaemia; LAMB, liposomal amphotericin B; NHL, non-Hodgkin lymphoma; SAA, severe aplastic anaemia.
[a]Two patients of the LAMB group and six patients of the historical control group were analysed for both primary and recurrent malignancy (indicated by *).
[b]Only 184 episodes were included in the analysis, as allergic reactions occurred in three patients during the first administration of LAMB.
, * Represents a patient who was analyzed during both primary disease and relapse (as indicated in a).

Fisher's exact test was used for subgroups where appropriate. All statistical tests were two-sided, and a p-value ≤0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 44 patients (24 boys; median age, 7.7 years) received at least one dose of LAMB for antifungal prophylaxis; two patients were included twice in the analysis, because they received antifungal prophylaxis for both primary and recurrent malignancy (Table 1). The median durations of the 184 analysed prophylaxis episodes and of neutropenia (absolute neutrophil count <500/μL) were 24 and 10 days (range, 5–104 days, and 0–52 days), respectively. Prolonged neutropenia (>10 days) was observed in 126 of the analysed episodes (68%) (Table 1).

Safety and tolerability

Antifungal prophylaxis with LAMB was prematurely discontinued in four patients (9%), because of allergic reactions. Whereas mild skin reactions (grade I/II) during the first administration were noted in three patients, a systemic grade III reaction occurred during the third administration of LAMB in one patient. All other clinical adverse events, such as fever, nausea, vomiting, or pain, were considered to be unrelated to the administration of LAMB.

The median level of creatinine at baseline was 0.33 mg/dL (range, 0.06–1.4 mg/dL), and was significantly lower than the maximum level during LAMB prophylaxis (median (range), 0.45 mg/dL (0.1–1.49 mg/dL), p <0.001), but comparable to the first level assessed after discontinuation of LAMB prophylaxis (median (range), 0.35 mg/dL (0.06–1.4 mg/dL), p 0.39) (Fig. 1). In seven episodes with normal baseline creatinine, levels were above 1.0 mg/dL at the end of treatment (grade I/II, n = 6 (3.2%); grade III/IV, n = 1 (0.5%)). In the only patient with an elevated creatinine level at baseline, the level remained increased at the end of treatment (1.21 and 1.38 mg/dL, respectively). Hypokalaemia (<3.0 mmol/L) occurred in 25 of the 184 prophylactic episodes (13.5%); however, hypokalaemia grade IV (<2.5 mmol/L) was seen in three cases only. Potassium was substituted in 21 and seven cases, orally and intravenously, respectively; one patient was hospitalized because of severe hypokalaemia.

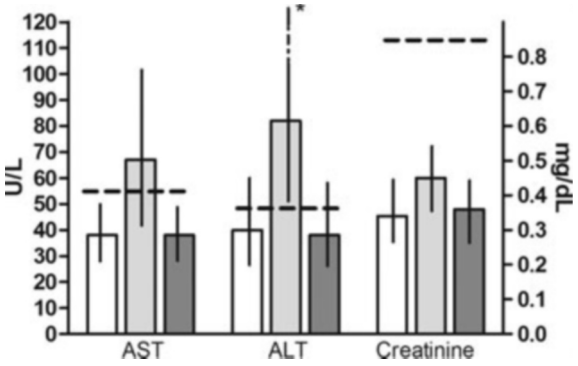

FIG. 1. Median plasma levels of aspartate transaminase (AST), alanine transaminase (ALT) and creatinine at baseline (white columns), maximum values during prophylaxis with liposomal amphotericin B (LAMB; light grey columns), and at end of treatment with LAMB (dark grey columns). The error bars represent the 25th and 75th quartiles, respectively. The horizontal dashed lines represent the upper range of normal values in healthy individuals. For all parameters assessed, baseline values and end-of-treatment values did not differ significantly, whereas maximum levels were significantly higher than baseline and end-of-treatment values (p <0.001 each). *165 U/L.

Maximum levels of the hepatic transaminases aspartate transaminase (AST) and alanine transaminase (ALT) during LAMB prophylaxis (median (range), 59 U/L (19–1819 U/L) and 83 U/L (17–2892 U/L), respectively) were significantly higher than baseline levels (median (range), 38 U/L (13–229 U/L) and 38 U/L (5–456 U/L), respectively; p <0.001 each) and than levels at end of treatment (median (range), 37 U/L (5–185 U/L) and 37 U/L (8–375 U/L), respectively; p <0.001 each) (Fig. 1). Levels of AST and ALT assessed at end of treatment did not significantly differ from baseline levels (p 0.48 and p 0.14, respectively).

Efficacy

After a median follow-up of 29 months after diagnosis (range, 6–119 months), 36 patients of the LAMB group were alive (81.8%). Eight patients died because of relapse or progression of the malignancy. Breakthrough IFD, defined as probable or proven IFD, did not occur in any patient while on prophylaxis (Table 2). In one patient suffering from AML, possible IFD was diagnosed. Febrile neutropenia occurred in 28 patients (68%) and in 57 of 184 antifungal prophylaxis episodes (31%) (Table 2). In 13 patients (32%) and 19 of the 184 prophylactic episodes (10%), empirical antifungal therapy was instituted (Table 2).

TABLE 2. Infectious complications in patients receiving prophylaxis with liposomal amphotericin B (LAMB) and in historical controls

	Patients with LAMB prophylaxis, no. (%)	Historical controls, no. (%)	p	
Total				
Patients[a]	41	39		
Cases[a]	43	45		
Episodes	184	201		
Proven IFD				
Patients	0	5 (13)	NS	
Cases	0	5 (11)	NS	
Probable IFD				0.01
Patients	0	2 (5)	NS	
Cases	0	2 (4)	NS	
Possible IFD				
Patients	1 (2)	5 (13)	NS	
Cases	1 (2)	5 (11)	NS	
Febrile neutropenic episode				
Patients	28 (68)	33 (84)	NS	
Cases	28 (65)	38 (76)	0.05	
Episodes	57 (31)	80 (40)	NS	
Empirical antifungal therapy				
Patients	13 (32)	15 (38)	NS	
Cases	13 (30)	18 (40)	NS	
Episodes	19 (10)	25 (12)	NS	

IFD, invasive fungal disease; NS, not significant.
[a]Several patients were included twice in the analysis, as they presented with *de novo* malignancy and with relapse; note that only 41 patients (43 cases) of the LAMB group were included in the analysis of infectious complications, as three patients were excluded because of allergic reactions during the first administration of LAMB.

Assessment of LAMB levels

In a randomly selected subset of the patients (n = 5), LAMB trough and peak levels were determined after a median of 35 dosages of LAMB (range, 15–66). The median trough and maximum levels were 0.64 μg/mL (range, 0.22–6.19 μg/mL) and 27.5 μg/mL (range, 24.4–56.2 μg/mL), respectively.

Comparison with the historical control group

A total of 39 patients (22 boys; 201 analysed episodes) were included in the historical control group. Six patients were included twice in the analysis for primary disease and relapse (Table 1). Twenty-four months after diagnosis, 26 patients of the historical control group (66.6%) were alive, and 13 patients (33.3%) had died because of their underlying disease. The median age of the patients was 10 years, and the median duration of neutropenia per analysed episode was 12 days, and thus comparable to the patients of the LAMB cohort. In 100 of the 201 analyzsed episodes (50.7%), no systemic antifungal prophylaxis was given, whereas fluconazole or itraconazole was administered in 19 (9.5%) and 80 (39.8%) of the episodes, respectively. Serum levels of itraconazole were not routinely assessed at that time.

Five proven and two probable IFDs were observed in the historical control group (Table 2). Specifically, proven/probable IFDs consisted of invasive aspergillosis (AML (n = 3), ALL and non-Hodgkin lymphoma (n = 1 each)), cryptococcosis (AML (n = 1)), and infection caused by *Absidia corymbifera* (severe/very severe aplastic anaemia (n = 1)). Proven/probable IFDs occurred in six patients not receiving antifungal prophylaxis and in one patient receiving itraconazole prophylaxis. Possible IFDs were seen in five historical controls. Importantly, the incidence of proven/probable IFD was significantly higher in historical controls than in the study population with LAMB prophylaxis (0 vs. 7; p 0.01) (Table 2). In contrast, the institution of empirical antifungal therapy was comparable in both cohorts.

Calculation of the total acquisition cost of antifungal compounds for both prophylaxis and therapy demonstrated that the average costs per kilogram body weight or per paediatric patient weighing 25 kg were €205 (±€129) and €5125 (±€3225) in the LAMB prophylaxis group, and €170 (±€380) and €4250 (±€9500) for control patients (p 0.08).

Discussion

The results of this prospective cohort analysis suggest that administration of LAMB twice weekly at a dosage of 2.5 mg/kg is feasible and well tolerated, and is an effective preventive antifungal approach for paediatric cancer patients at high

risk for IFD. In our study population, LAMB was prematurely discontinued in four patients (9%), because of infusion-related reactions Whereas the discontinuation rate in a randomized study in adults who received 50 mg of LAMB every other day as a 1-h infusion was 2.8% [14], similar or higher rates of premature discontinuation were reported in children receiving prophylactic LAMB at a dosage of 1 mg/kg as a 30-min infusion (19%), as well as in children receiving oral itraconazole (11%) or voriconazole (18%) as antifungal prophylaxis [15–17]. Notably, the use of mould-active antifungal triazoles such as itraconazole or voriconazole for prophylaxis in children is limited by the interaction with vinca alkaloids, which constitute a cornerstone in the treatment of paediatric leukaemia [5,6]. In addition, a recent survey reported on low compliance of children on itraconazole prophylaxis [18]. Echinocandins are associated with fewer side effects [19–21] than LAMB. However, because of the short half-life, echinocandins have to be given intravenously on a daily basis, which is not feasible in children suffering from acute leukaemia, who, to a large extent, receive chemotherapy in an outpatient setting.

The high frequency of abnormalities in laboratory values in our group of high-risk patients while on LAMB prophylaxis was expected, given the serious nature of their underlying disorders and the multitude of concomitant medications. However, median end-of-treatment values of AST and ALT did not significantly differ from their respective baseline values, and only a minority of patients had mildly elevated creatinine values at end of treatment. Similarly, hypokalaemia was usually mild, requiring hospitalization of one patient only. These observations are in line with previous reports on LAMB prophylaxis in paediatric and adult patients [14,15].

In our high-risk population, characterized by a median duration of neutropenia of 10 days per episode, no proven or probable IFD occurred, and pulmonary infiltrates compatible with invasive mould infection were seen in only one patient. This is in line with the findings in 16 children receiving LAMB (1 mg/kg) and in 74 adult transplant recipients receiving LAMB (2 mg/kg) three times weekly [15,22]. Our observation is also supported by a prospective, randomized, open-label trial in adults with haematological malignancies and prolonged neutropenia, in which patients receiving 50 mg LAMB every other day experienced significantly less proven/probable IFD than patients without systemic antifungal prophylaxis [14]. Although the regimens of LAMB differed between these studies, the assessment of trough samples in our patient population demonstrated that LAMB plasma concentrations 4 days after the last infusion were close to the MIC_{90}s for susceptible strains (*Candida*, 0.25–1 mg/L; *Aspergillus*, 0.5–2 mg/L), indicating that twice-weekly dosing as described in our study may provide useful protection against fungal infections [9,23]. However, it is important to note that MICs for amphotericin B have not correlated well with clinical outcome when studied.

Unfortunately, a comparison of our results with reports on other antifungal strategies in children is hampered by different inclusion criteria and different study endpoints. For example, one prospective observational study analysing 44 episodes of prophylactic itraconazole in 39 paediatric cancer patients did not report on breakthrough infection, but this study included low-risk patients such as children with brain tumours or Langerhans cell histiocytosis, who are considerably less immunocompromised than our study population [16]. It is important to note that most of the few reports on antifungal prophylaxis in children are observational studies without a comparison with a control group [15–17,24]. Therefore, because of the difficulties in performing well - designed and sufficiently powered randomized studies on antifungal prophylaxis, particularly in children, a comparison with a historical control group might be a reasonable approach [25]. Although we recognize the limitation of this approach, we has to emphasize that our historical control group was comparable to the study population with regard to patient characteristics, chemotherapeutic regimens, diagnostic procedures, and supportive care measures, except for the systemic antifungal prophylaxis analysed. In addition, other parameters, such as the extent of construction work, which is known to increase the risk for invasive aspergillosis, did not differ between the two time periods analysed [26]. Whereas the incidence of proven/probable IFD in the historical controls is in line with the reported risk of IFD in this patient population [1], it is significantly higher than the incidence of IFD in our study population, indicating that LAMB prophylaxis is effective, and the calculation of the number needed to treat results between nine and 11, depending on the inclusion of possible IFD. Importantly, as the individual genetic profile was demonstrated to influence the risk and severity of infectious complications [27,28], we performed the analysis with the number of patients as denominator. Whereas prophylactic LAMB twice weekly seems to decrease the incidence of proven/probable IFD in paediatric high-risk patients, the incidence of empirical antifungal therapy was unaffected.

In contrast to adults, where significant cost savings were obtained by the institution of LAMB prophylaxis [29], our data demonstrate that the costs of antifungal compounds were comparable in the study population and historical controls. However, it is important to note that we included in our analysis only acquisition costs of antifungal medication. As LAMB

prophylaxis was usually administered in an outpatient setting (except for the time when the patient was admitted to the hospital for chemotherapy or for complications such as febrile neutropenia), intermittent LAMB prophylaxis might improve quality of life and ultimately reduce cost.

In conclusion, LAMB prophylaxis at a dosage of 2.5 mg/kg twice weekly is feasible and safe, and appears to be effective in preventing IFD in paediatric cancer patients at high risk. On the basis of the data generated in this cohort study, this approach is a reasonable alternative for antifungal prophylaxis in patients in whom other agents are not appropriate.

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Transparency Declaration

T. Lehrnbecher has received grants from Gilead, is a consultant to Astellas, Gilead, Merck, Sharp & Dohme, and Schering-Plough, and served at the speakers' bureau of Astellas, Gilead, Merck, Sharp & Dohme, and Schering-Plough. A. H. Groll has received grants from Gilead and Merck, Sharp & Dohme; is a consultant to Astellas, Gilead, Merck, Sharp & Dohme, and Schering-Plough, and served at the speakers; bureau of Astellas, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough, and Zeneus/Cephalon. All other authors: nothing to declare.

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