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Prophylactic use of liposomal amphotericin B in children and adolescents undergoing allogeneic hematopoietic cell transplantation: A 10-years single center experience

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ABSTRACT

Background: Azoles are recommended as antifungal prophylaxis in decreasing the incidence of invasive fungal disease (IFD) in high-risk patients in pediatric oncology, including patients receiving allogeneic hematopoietic cell transplantation (HCT). However, azole related toxicity, pharmacological interactions with immunosuppressive medication and conditioning regimen and growing incidence of azole resistance makes this antifungal agent not ideal in the transplant setting. This study reports on the contemporary incidence and outcome of IFD after allogeneic HCT in children with prophylactic liposomal amphotericin B (L-AMB).
Methods: This single-center retrospective study included all patients transplanted between 2012 and 2022. Primary endpoint was the incidence of IFD until hospital discharge post-transplant. Secondary aims were the incidence of IFD and survival 180 days after allogeneic HCT, the evaluation of toxicity of L-AMB and further risk factors for development of IFD during antifungal prophylaxis. Descriptive statistics were performed.
Results: 161 pediatric patients received L-AMB. Incidence of breakthrough IFD post-transplant was 7.5 % (12/161). The 12 cases comprised of three invasive yeast infections (1.9 %), three probable (1.9 %) and six possible (3.7 %) mold infections. Adverse events were in 22.4 % of the patients, most of them mild and reversible. Discontinuation of L-AMB occurred in 2.5 % (4/161) of the patients due to severe hypersensitivity reactions.
Conclusions: The risk of breakthrough IFD in pediatric patients undergoing allogeneic HCT under L-AMB prophylaxis is comparable with the reported risk under first line recommendation drugs for antifungal prophylaxis. If no hypersensitivity reaction occurs, L-AMB is tolerated with manageable side effects. This antifungal agent should therefore be considered as an alternative option to azoles in pediatric allogeneic HCT recipients.

1. Introduction

Invasive fungal disease (IFD) is a serious problem in pediatric patients after allogeneic hematopoietic cell transplantation (HCT) and still contributes to a significant level of morbidity and mortality. Therefore, antifungal prophylaxis is recommended to reduce the incidence of IFD and fungal-related mortality. As an example, in the study of Czyżewski et al., the incidence of IFD in an allogeneic HCT setting decreased significantly (from 27 % to 11.7 %) after the introduction of antifungal prophylaxis [1]. Although incidence rates of IFD with use of antifungal prophylaxis are lower, they still range from 5 % to nearly 20 % post-transplant [2–6]. This wide range in incidences can be explained by different patient characteristics, the use of various prophylactic antifungal strategies, IFD definitions in studies and local fungal epidemiology.

Current evidence-based guidelines recommend azole antifungal prophylaxis with mold activity in the allogeneic HCT setting [7,8]. However, using azole prophylaxis raises concerns due to inter- and intra-patient variability in plasma concentration, azole-related toxicity, pharmacological interactions with immunosuppressive medication,

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interaction-based toxicity with conditioning regimen and growing incidence of azole resistance [9]. Alternatives for azole antifungal prophylaxis are echinocandins or polyenes [6,10–12]. The use of echinocandins as antifungal prophylaxis is currently incorporated in some guidelines for pediatric cancer patients and allogeneic HCT recipients [7,8,13]. However, the use of L-AMB as antifungal prophylaxis in allogeneic HCT setting is not encouraged due to the scarcity of studies. Due to the abovementioned objections to the prophylactic use of azoles and the positive findings of an alternative prophylaxis in high-risk pediatric cancer patients as discussed by Bochennek et al. we used liposomal amphotericin B (L-AMB) preferentially as antifungal prophylactic regimen in our institution since 2012 [14]. L-AMB is a polyene antifungal agent with a much improved toxicity profile compared with conventional amphotericin B deoxycholate [15].

In this retrospective study, we evaluated the incidence and outcome of IFD after allogeneic HCT with prophylactic L-AMB in our pediatric cohort.

2. Methods

2.1. Study design and inclusion criteria

This retrospective study was executed at the Wilhelmina Children's Hospital and Princess Máxima Center in Utrecht between January 2012 and June 2022. We included all pediatric patients who underwent an allogeneic HCT, except for children with a metabolic disease and Fanconi anemia, as those were considered to be at low risk for IFD. Primary prophylaxis was defined as antifungal prophylaxis given to a child without a history of IFD. Secondary prophylaxis was defined as antifungal prophylaxis given to a child after earlier treatment for IFD. Only patients with a history of IFD up to six months prior to transplantation were included.

2.2. Transplantation and supportive care

In our allogeneic HCT setting, L-AMB is the preferred antifungal prophylaxis of choice. Prophylactic antifungal treatment with L-AMB is intravenously twice weekly (2.5 mg/kg). Patients with an allergic or hypersensitivity reaction to L-AMB received an azole or echinocandin as alternative prophylaxis. Patients received antifungal prophylaxis from the start of conditioning until immune recovery (CD3 recovery >300cells/uL; CD4 > 200 cells/uL).

All patients were monitored for IFD with a serum galactomannan test twice a week during neutropenia and weekly until immune recovery. In case of suspected IFD, for example prolonged neutropenic fever, a repeated positive serum galactomannan test or in case of respiratory symptoms, a CT- chest was made. A broncho alveolar lavage (BAL) was indicated in case of suspected fungal lesions on imaging. The BAL provided material for a galactomannan test, microbiological and molecular diagnostics. Phenotypic susceptibility testing was performed for azoles, echinocandins and polyenes. Antifungal susceptibility testing was performed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST), using microbroth dilution in a 96 wells plate. Results were interpret using breakpoints provided by EUCAST. Genotypic susceptibility testing was only performed for azole antifungals. An RT-PCR of *A. fumigatus* was performed which also tested for the tr34/l98h and tr46/y121f/t289a genotypes. When a pulmonary IFD was suspected or in case of specific symptoms leading to the suspicion of cerebral IFD or fungal sinusitis, additional imaging (MRI) of brain and sinuses was performed.

Conditioning regimens were applied according to standard protocols. A conditioning regimen consisting of fludarabine, clofarabine and exposure-targeted busulfan (90 mg*h/L) was mainly used for malignant indications [16,17]. for bone marrow failure patients, it was based on international EWOG MDS/SAA protocols. Patients with primary immunodeficiency were conditioned with fludarabine and exposure-targeted busulfan (90 mg*h/L). In cases transplanted with an unrelated donor, serotherapy with anti-thymocyte globulin was added to the conditioning regimen. All cord blood patients received 10 ug/kg granulocyte colony-stimulating factor (G-CSF) from day seven after allogeneic HCT until neutrophils were >2000/μL. GvHD prophylaxis and treatment was according to standard protocols. Ex vivo T cell depletion was very rarely used. The transplant facility uses HEPA filtered air in all patient rooms.

2.3. Outcomes

The main objective was to evaluate the incidence of IFD until hospital discharge post-transplantation (median of 30 days). In our institution, L-AMB was switched to oral voriconazole if adequate immune recovery had not been reached at the time of hospital discharge. Other objectives were the incidence of IFD and survival 180 days after allogeneic HCT, to identify further risk factors for development of IFD during antifungal prophylaxis, as well as to report on toxicity related to antifungal prophylaxis with L-AMB. Therefore, the number and severity (CTCAE version 5.0) of clinical and laboratory adverse events were retrospectively reviewed from the day-to-day patient notes, from start of conditioning until hospital discharge. We identified patients, who developed proven, probable, or possible IFD using the definitions of the EORTC/MSG Consensus Group [18]. Age at allogeneic HCT, gender, prior history of IFD, indication for allogeneic HCT, donor relation and match grade, conditioning regimen, transplant number, duration of neutropenia and GVHD were considered risk factors related to the occurrence of IFD [19,20].

2.4. Data and statistics

Our center uses an electronic database (TRIASUS) for prospective data collection of all our transplants. For this retrospective analysis, additional data on IFD and data on toxicity were obtained from the electronical medical records of each patient individually. Data collection and processing were in accordance with Dutch law for patient confidentiality and the Declaration of Helsinki (2013 version). For use of data in this retrospective study we refer to local IRB biobank trial numbers 05/143 and 11/063-K. Descriptive statistics were performed for the baseline characteristics of the studied population and incidence of fungal infections. Relevant risk factors influencing the occurrence of IFD were examined using Cox proportional hazard models. Survival curves were measured using the Kaplan Meier method. SPSS (version 26) was used for statistical analysis.

3. Results

3.1. Baseline characteristics

Hundred fifty-seven pediatric patients received 161 allogeneic HCTs between January 2012 and June 2022. There were 95 boys and 66 girls (Table 1). The age at conditioning ranged from four months to 20 years old (median: 9.5 years old). Forty-four patients (27.3 %) had acute lymphoblastic leukemia (ALL), 42 (26.1 %) had acute myeloid leukemia (AML) and 25 had other malignant diseases (e.g. juvenile myelomonocytic leukemias, lymphomas, chronic myeloid leukemias). There were 51 nonmalignant indications for allogeneic HCT. This group comprised of primary immunodeficiencies (14, 8.7 %), 34 bone marrow failure syndromes (i.e. severe aplastic anemia (SAA) (13, 8.1 %), myelodysplastic syndromes (14, 8.7 %) and other bone marrow failure syndromes (7, 4.3 %) like dyskeratosis congenita and congenital neutropenia. One auto-immune disease (relapsing polychondritis after failure of multiple lines of immunosuppressive therapy including autologous transplant) and one other (epidermolysis bullosa with extensive skin blistering and suspected fungal colonization). Most patients had a first allogeneic HCT (145/161, 90.1 %); some received a second (15/161, 9.3 %) or third

Table 1
Baseline characteristics of pediatric patients receiving an allogeneic HCT.

No. patients	161
Gender, n (%)	
Male	95 (59)
Female	66 (41)
Underlying disease, n (%)	
Malignant	44 (27.3)
ALL	42 (26.1)
AML	25 (15.6)
Other	34 (21.1)
Non-malignant	13 (8.7)
Bone marrow failure syndromes	1 (0.6)
Primary immunodeficiency	1 (0.6)
Auto-immune disease	
Age at HSCT, years, median (range)	9.5 (0.3–20.4)
Source of stem cells, n (%)	
Cord blood	83 (51.6)
Bone marrow	74 (45.9)
- Sibling	37 (50)
- Matched Unrelated Donor	37 (50)
Peripheral blood	4 (2.5)
Conditioning regimen, n (%)	
Myelo ablative	140 (87)
Non-myeloablative	21 (13)
Neutrophilic engraftment, days, median (range)	
Cord blood	17.9 (9–44)
Bone marrow	23 (15–53)
Peripheral blood	11 (10–12)

transplantation (n=2). In total, four patients were included twice and one patient was included three times. Eighty-three (51.6 %) patients received cord blood transplantation, 74 (45.9 %) bone marrow and 4 patients peripheral blood stem cells. The incidence of acute GVHD in this study cohort was 36.6 % (59/161) with 35.6 % (21/59) of the pediatric patients with acute GVHD having a severe GVHD grade 3–4.

3.2. Fungal infections: incidence and outcome

The cumulative incidence of breakthrough IFD after allogeneic HCT at hospital discharge from transplant in this retrospective cohort was 7.5 % (12/161) with a median duration of L-AMB prophylaxis of 30 days (inter quartile range 23–39). The 12 cases comprised of three invasive yeast infections (1.9 %) and nine mold infections: three probable (1.9 %) and six possible pulmonary mold infections (3.7 %) (Table 2). All yeast infections were *Candida* bloodstream infections. None of the three isolated *Candida* species as well as the cultured molds were resistant to L-AMB. Most patients developed an IFD in the first weeks before engraftment (n=11). One patient developed an IFD after engraftment, in the context of immunosuppressive treatment for allo-immune lung disease. One of the 12 patients, who developed a breakthrough IFD, received secondary antifungal prophylaxis. The incidence of IFD 180 days after allogeneic HCT was 9.3 % (15/161). These three late IFD cases occurred in the context of immunosuppressive treatment for severe GVHD. Two of these patients were back again on L-AMB prophylaxis during secondary admission (in the outpatient clinic they received standard voriconazole as antifungal prophylaxis), one patient was on posaconazole prophylaxis. Fifty-four of 161 patients (33.5 %) were still on antifungal prophylaxis at 180 days after HCT.

Of the IFD patients, 10/15 (66.7 %) survived; while 128/147 (87.1 %) non-IFD survived (Fig. 1, p=0.05). None of the IFD patients died of IFD directly, but all of other transplant-related causes (Table 2).

Possible further risk factors for the occurrence of IFD in this patient

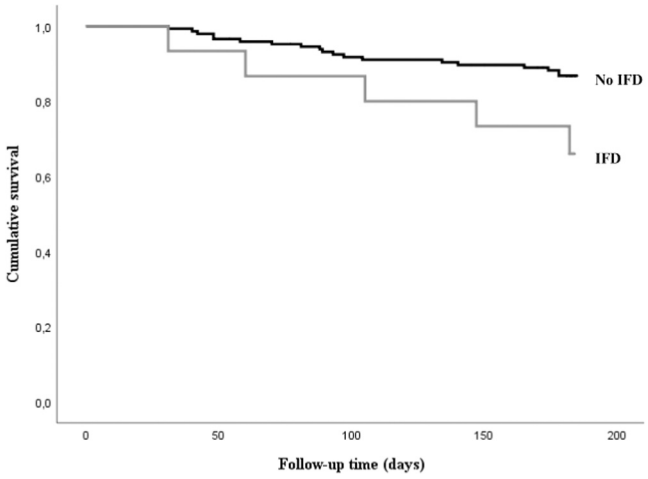

Fig. 1. Half-year overall survival curve of pediatric patients undergoing allogeneic HCT using the Kaplan Meier survival method.

Table 2
Characteristics of breakthrough IFD.

		Disease	Antifungal prophylaxis	Definition	Localization	Timing IFI (days after HCT, engrafted)	Suspected pathogen	Therapy	Outcome
Invasive mold infection									
1	♀ 2 years	SCID	L-AMB	Probable	Lung	25, pre-engraftment	*Aspergillus non fumigatus*	L-AMB, caspofungin	Death
2	♂ 6 years	AML	L-AMB	Probable	Lung	1, pre-engraftment	*Penicillium* species	L-AMB	Alive
3	♂ 4 years	SAA	L-AMB	Possible	Lung	9, pre-engraftment	-	L-AMB	Alive
4	♂ 1 year	CID	L-AMB	Possible	Lung	27, post-engraftment		L-AMB	Death
5	♀ 17 years	Hodgkin	L-AMB	Possible	Lung	17, pre-engraftment	-	L-AMB	Death
6	♂ 8 years	ALL	L-AMB	Possible	Lung	16, pre-engraftment	-	Voriconazole	Alive
7	♂ 15 years	ALL	L-AMB	Possible	Lung	21, pre-engraftment	-	Voriconazole	Alive
8	♂ 15 years	AML	L-AMB	Probable	Lung	15, pre-engraftment	Positive galactomannan; BAL PCR negative	Voriconazole; caspofungin	Alive
9	♀ 9 months	ALL	L-AMB	Possible	Lung	13, pre-engraftment	-	Voriconazole	Alive
Invasive yeast infection									
10	♀ 14 years	SAA	L-AMB	Proven	Bloodstream	12, pre-engraftment	*Candida parapsilosis*	Fluconazole, line removal	Alive
11	♂ 18 years	ALL	L-AMB	Proven	Bloodstream	16, pre-engraftment	*Candida kefir*	L-AMB; line removal	Alive
12	♀ 18 years	ALL	L-AMB	Proven	Bloodstream	13, pre-engraftment	*Candida parapsilosis*	Micafungin, line removal	Death

SCID indicates severe combined immunodeficiency; CGD, chronic granulomatous disease; CID, combined immunodeficiency; DLBCL, Diffuse large B-cell lymphoma.

group considered were age at allogeneic HCT, gender, indication, prior history of IFD, donor relation and match grade, conditioning regimen and transplant number. In univariate analysis, only donor-relation (p=0.023) was identified as a possible risk factor for the occurrence of IFD in this study-cohort (supplementary table 1).

3.3. Toxicity

Most patients receiving L-AMB did not have any side effects (125/161, 77.6 %). The most common adverse effect was the need for potassium supplementation due to hypokalemia in 13 % of patients, which was usually mild and always reversible. An allergic or hypersensitivity reaction occurred in ten patients (6.2 %); this was CTCAE grade 3 in 4/10, which warranted an immediate switch to another antifungal prophylactic strategy prior to transplant. L-AMB is known for causing some degree of nephrotoxicity, which was usually mild when given twice a week. In this cohort, severe renal toxicity (in the context of a CTCAE grade 3) occurred in seven patients (4.3 %). In 3/7 patients, L-AMB was therefore switched to another antifungal prophylactic treatment.

4. Discussion

This retrospective study reported on the incidence and outcome of IFD in a pediatric cohort of allogeneic HCT recipients with prophylactic L-AMB as the use of mold active azoles in this patient group is hampered by drug-drug interactions, erratic plasma exposure and toxicity. In our cohort, the cumulative incidence of breakthrough IFD until hospital discharge was 7.5 %.

It is difficult how this result aligns with previous studies. In the literature, the incidence of IFD has varied from study to study depending on the studied population, IFD definitions, used antifungal prophylactic strategy and different measures for IFD incidences. It is particularly difficult to draw stringent conclusions on the effectiveness of different antifungal prophylactic strategies from non-randomized studies.

Despite these obstacles, a few studies reported on IFD incidences with mainly prophylactic amphotericin B in the pediatric transplant setting (Table 3) [3,5,6,10,11,21]. Although all these studies used different prophylactic L-AMB regimens, different classifications of IFD and follow-up time, we can conclude that the overall incidence of IFD with prophylactic L-AMB in this retrospective study falls within range. Furthermore, to our knowledge, this is the largest cohort evaluating the incidence and outcome of IFD in pediatric HCT recipients with L-AMB as antifungal prophylaxis.

Recently, a clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and HCT recipients was developed in an attempt to facilitate evidence-based clinical care. This guideline weighed the risks and benefits of the different options regarding IFD management based on all available literature [13]. The authors in the guideline formulated a recommendation against the use of prophylactic amphotericin B. One of the reasons was because of lacking good-quality evidence studies examining the efficacy of the liposomal variant of amphotericin B. Azoles are still the first line recommendation in the prevention of IFD in the allogeneic HCT setting [7]. This is also the recommendation according to the CPG guideline. Having a closer look at two studies that examined a mold-active azole as prophylaxis in the allogeneic HCT setting, the incidence rates of breakthrough IFD of those studies are comparable with the percentage of breakthrough IFD we observed [22,23]. The first study (Wingard et al.) [22] compared prophylactic voriconazole versus fluconazole, in a multicenter randomized double-blind design, in HCT recipients (adults and children). The cumulative incidence rate of IFD for voriconazole prophylaxis was 7.3 % at 180 days. The second study (Ullmann et al.) [23] compared prophylactic posaconazole versus fluconazole in patients (adults and adolescents) with graft versus host disease and receiving immunosuppressive therapy in an international randomized double-blind trial. An incidence rate of 5.3 % was found for posaconazole in preventing IFD.

Regarding the toxicity in our study cohort, we found that L-AMB can be considered tolerable with a dosage of 2.5 mg/kg twice weekly. There were adverse events in 22.4 % of the patients, most of them mild and reversible. In 13 patients (8.1 %) L-AMB had to be discontinued due to serious adverse events. Hypersensitivity reactions to L-AMB were the main reason for discontinuation. This finding is in line with the literature reporting low discontinuation rates for L-AMB prophylaxis at doses up to 3 mg/kg/day, whereas higher doses led to higher withdrawal rates [10,11,14,21,24,25]. Although L-AMB is known for causing some degree of nephrotoxicity, the etiology of the creatinine disturbances was always multifactorial in origin due to concomitant nephrotoxic medications, including calcineurin inhibitors and antivirals.

Based on our results, children who developed IFD had higher all-cause mortality compared with those who did not. This has also been reported in previous studies [26,27]. However, the impact of IFD on survival is difficult to ascertain in the absence of prospective studies and is influenced by several factors like underlying disease, transplant procedure and the need for immunosuppressive medication as is with the occurrence of GVHD.

In conclusion, prophylaxis with L-AMB twice a week seems to be comparable in efficacy with azoles, which are the first line recommendation for antifungal prophylaxis. If no hypersensitivity reactions occur, L-AMB is tolerated with manageable side effects. Therefore, L-AMB can be considered a decent alternative prophylaxis to azoles in the

Table 3
Studies evaluating L-AMB as antifungal prophylaxis in pediatric HCT patients.

Author, year	Study type	Patients (number, type)	Antifungal prophylaxis	Breakthrough IFD (percentage, classification, follow-up time)
Kobayashi 2008 [3]	Retrospective, single center	334 patients with malignant and nonmalignant conditions who received chemotherapy, immunosuppressive treatment, or HCT	Oral amphotericin B (100 mg/kg/day) before March 2005. Intravenously micafungin (1 mg/kg/day) after March 2005 from the start of conditioning until neutrophil recovery	6.9 %, proven/probable/possible cases
Lehrnbercher, 2019 [5]	Prospective, multicenter study	304 patients with leukemias, non-Hodgkin lymphomas, or HCT	L-AMB or azoles	5.8 %, proven/probable cases, first 100 days post-transplant
Bui 2019 [6]	Retrospective, single center	84 patients, HCT	L-AMB (3–10 mg/kg/weekly), voriconazole or micafungin	2.08 per 1000 prophylaxis days, proven/probable/possible
Mendoza-Palomar 2020 [10]	Retrospective, single center	118 patients, HCT	L-AMB (1 mg/kg/day) intravenously daily	8 %, proven/probable cases, first 90 days post-transplant
Roman 2007 [11]	Prospective, single center	51 patients, HCT	Daily L-AMB (3 mg/kg/day)	9.7 %, proven yeast infections/no mold infections, first 100 days post-transplant
Tollemar 1993 [21]	RCT, single center	76 patients (children and adults), HCT	L-AMB (1 mg/kg/ daily) vs placebo	2.8 % vs 7.5 %, proven cases

allogeneic HCT setting, but transplanters should remain vigilant as to whether L-AMB is the right option for each patient. To determine the most beneficial prophylaxis with least toxicity, L-AMB should be compared with an echinocandin and/or an azole in a randomized study in the future.

Ethical approval

No specific ethical approval for this retrospective study was required. For use of data in this retrospective study, there is patient informed consent within local data and biobank access committee protocols (IRB biobank trial numbers 05/143 and 11/063-K).

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CRediT authorship contribution statement

Marc B. Bierings: Writing – review & editing. **Tom F.W. Wolfs:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Caroline A. Lindemans:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Laura G.Y. Rotte:** Writing – original draft, Investigation, Formal analysis. **Coco C.H. de Koning:** Methodology, Formal analysis. **Yvette G.T. Loeffen:** Writing – review & editing, Investigation. **Jaap Jan Boelens:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100175.

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