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.