Safety, tolerance and outcome of treatment with liposomal amphotericin B in paediatric patients with cancer or undergoing haematopoietic stem cell transplantation

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Objectives: To assess safety, tolerance and efficacy of liposomal amphotericin B (LAMB) in a large unselected series of paediatric cancer/haematopoietic stem cell transplantation (HSCT) patients requiring LAMB therapy.

Patients and methods: The study included 84 children and adolescents (median age: 11 years) who received 141 consecutive courses of LAMB for prophylaxis (32), empirical therapy (83), possible (19) or probable/proven (7) invasive infections. LAMB was administered until intolerance or maximum efficacy at dosages individually determined by the responsible physician.

Results: Fifty-nine courses were post-HSCT (42%, 49 allogeneic), and 92 courses were started during granulocytopenia (65%). The median duration of LAMB therapy was 13 days (range 1–79), and the median maximum dosage was 2.8 mg/kg (range 0.93–5.10). Mild-to-moderate adverse events were noted during 109 courses (77%; hepatic, 58.8%; electrolyte wasting, 52.5%; renal, 31.9%; infusion-related reactions, 8.5%); adverse events necessitating discontinuation of LAMB occurred in 6 courses (4.3%; renal, 3; anaphylaxis, 2; hepatic, 1). While median hepatic transaminase, alkaline phosphatase and blood urea nitrogen values were slightly ($P<0.01$) higher at end of treatment (EOT), bilirubin and creatinine values were not different from baseline. Complete or partial responses were observed in 16/19 and 2/7 courses for possible and probable/proven invasive infections. Thirty-two of 33 courses of prophylaxis and 74 of 83 courses of empirical therapy were completed with success. Overall survival was 90.8% at 3 months post-EOT.

Conclusions: LAMB had acceptable safety and tolerance and was useful in prevention and treatment in unselected, mostly granulocytopenic paediatric patients undergoing treatment for cancer or HSCT.

Keywords: antifungal agents, cancer, children, mycoses, stem cell transplantation

Introduction

Invasive fungal infections are an important cause of morbidity and mortality in severely immunocompromised children with cancer and following allogeneic blood stem cell transplantation. Despite advances in early diagnosis and the clinical development of new and effective antifungal agents, prevention and management of these infections continue to be challenging and overall mortality of affected patients remains unacceptably high. Only a few antifungal compounds are approved in paediatric

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patients, and there is very limited data on their safety and therapeutic outcomes in this distinct patient population.\textsuperscript{1,2}

The small unilamellar liposomal formulation of amphotericin B (LAMB) is approved for empirical antifungal therapy and treatment of invasive fungal infections based on recent data that showed equivalence to standard first-line treatment of invasive candidiasis and aspergillosis.\textsuperscript{3,4} Although the compound is approved in paediatric patients beyond the neonatal period, data on its use in children and adolescents, particularly outside the settings of clinical trials, are limited.\textsuperscript{5–9} We therefore analysed the safety, tolerance and therapeutic outcomes of LAMB in a large unselected, consecutive series of immunocompromised paediatric patients with cancer and/or hematopoietic stem cell transplantation (HSCT) requiring LAMB therapy.

**Patients and methods**

*Study design*

The study was a single-centre, non-comparative, prospective observational study and was conducted between September 2000 and August 2003. Patients eligible for inclusion had to be followed at the Department of Pediatric Hematology/Oncology and had received at least one dose of LAMB. 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 and/or HSCT that have been reviewed and approved by the institutional ethics committee. LAMB was administered intravenously at dosages individually determined by the responsible physician for prophylaxis, as empirical therapy, or as treatment of presumed or documented invasive fungal infections. The drug was infused as recommended by the manufacturer and continued until occurrence of intolerance, the end of the period at risk or the resolution of signs and symptoms of possible, probable or proven infection. Post-therapeutic follow-up was at least until 3 months after the end of treatment in cases of patient survival. Data collection was accomplished with a standardized case report form. The primary endpoint of the study was the assessment of safety and tolerance. Treatment success and mortality were secondary endpoints.

**Assessment of safety and tolerance**

Clinical treatment emergent adverse events (AEs) were recorded and graded according to current Common Terminology Criteria of Adverse Events set forth by the US National Cancer Institute\textsuperscript{10} and rated as possibly, probably or definitely related to treatment with LAMB. Laboratory parameters of renal and hepatic organ function were recorded at baseline and end of treatment (EOT). In addition, the most pathological value during treatment was assessed for each parameter and patient. As adjunct to the non-parametric comparison of baseline, maximum and EOT values, increases in laboratory parameters at EOT were also graded as increased to $\geq 1.5$ and $\geq 3.0$ times their respective baseline value (H. K. and A. H. G.). The diagnostic validity of invasive fungal infections was classified according to the EORTC/MSG criteria published in 2002.\textsuperscript{11} Responses to treatment in cases of possible, probable and proven invasive fungal infections were evaluated according to efficacy endpoints in recent clinical trials in invasive aspergillosis and candidiasis.\textsuperscript{12,13} A favourable response (‘success’) included either ‘complete response’ or ‘partial response’. The efficacy endpoint in patients receiving LAMB as empirical antifungal therapy or in prophylactic indication (‘success’) was defined as the absence of recurrent or breakthrough fungal infection, no discontinuation due to adverse events and survival at the time of discontinuation of the compound. Any fungal infection documented by imaging or microbiology during LAMB therapy was considered as breakthrough fungal infection and graded as failure.

**Statistical considerations**

Data were analysed by descriptive statistics unless indicated otherwise. Continuous data are presented as median values and ranges; for statistical comparisons, the Mann–Whitney U test or Kruskal–Wallis ANOVA was used. Relationships between parameters of drug exposure and adverse events were explored by non-parametric Spearman correlation analysis. $P<0.05$ was considered to be statistically significant.

**Results**

During the 3 year enrolment period, 141 separate courses of treatment with LAMB were administered to 84 patients. All 141 courses were included in the analysis. Forty-six (54%) of the 84 patients were male and 38 (46%) were female; the median age at the initiation of antifungal therapy was 11 years with a range of 0.2–20 years. The majority of patients (55; 65.5%) had a haematological malignancy as principal diagnosis, followed by solid tumours (17; 20.2%), bone marrow failure syndromes (11; 13.1%) and Langerhans cell histiocytosis (1; 1.2%).

In 83 of the 141 courses (58.9%), LAMB was administered as empirical therapy, in 32 (22.7%) as primary or secondary prophylaxis, in 19 (13.5%) as treatment for possible invasive fungal infection (possible invasive pulmonary aspergillosis) and in 7 (4.9%) as treatment for probable or proven invasive fungal infections [probable pulmonary (3) and disseminated (1) aspergillosis; candidaemia (3)]. Fifty-nine courses were administered post-HSCT (41.9%; 49 allogeneic), and 92 courses (65.2%) were started during profound granulocytopenia [absolute neutrophil count (ANC) $\leq 500$ cells/$\mu$L] that lasted for a median duration of 13 days (range 2–69 days) following the commencement of LAMB therapy. In the majority of courses (130/141; 92.2%), LAMB was administered as monotherapy. The median duration of treatment with LAMB was 13 days (range 1–79), and the median maximum daily dosage was 2.8 mg/kg [range 0.93–5.10; see Table S1 available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

A total of 220 treatment-emergent AEs were recorded during 109 courses (77%). Most AEs were of grade I or II; grade III or IV AEs leading to the discontinuation of LAMB occurred during six courses (4.3%; Table 1). The most commonly recorded AEs included elevated liver function parameters, electrolyte wasting...
Liposomal amphotericin B in paediatric cancer patients

Table 1. Treatment emergent adverse events during 141 courses of LAMB

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) of courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I or II adverse events:</td>
<td></td>
</tr>
<tr>
<td>hepatic</td>
<td>109 (77)</td>
</tr>
<tr>
<td>electrolyte wasting</td>
<td>83 (58.8)</td>
</tr>
<tr>
<td>renal</td>
<td>74 (52.5)</td>
</tr>
<tr>
<td>infusion-related reactions</td>
<td>45 (31.9)</td>
</tr>
<tr>
<td>Grade III or IV adverse events:</td>
<td></td>
</tr>
<tr>
<td>renal</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>anaphylaxis</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>hepatic</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>

LAMB, liposomal amphotericin B.

Figure 1. Course of laboratory parameters of renal and hepatic function during treatment with LAMB. Depicted are median values (horizontal line), the inter-quartile ranges (box) and the 10–90% percentiles (whiskers) of the entire series at baseline and at end of treatment and the maximum values observed during therapy. *P < 0.01 for the comparison of median end of treatment versus median baseline values by the Mann–Whitney U test. BUN, blood urea nitrogen; GOT, glutamate oxalate transaminase; GPT, glutamate pyruvate transaminase; Alk. Phos., alkaline phosphatase.

causing hypomagnesaemia and hypokalaemia, elevated renal function parameters and infusion-related reactions. Occurrence (P = 0.0035) and number (P = 0.0002) of AEs correlated with the weight-normalized cumulative exposure to LAMB but not with the weight-normalized maximum daily dose on treatment. Analysis of treatment-emergent AEs during the first episode of LAMB treatment showed similar rates when compared with the entire dataset [see Table S2 available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Increases in laboratory hepatic and renal function parameters during therapy were frequent. However, while median glutamate oxalate transaminase (GOT), glutamate pyruvate transaminase (GPT), alkaline phosphatase (AP) and blood urea nitrogen (BUN) values were slightly elevated at EOT (P ≤ 0.01), median bilirubin and median creatinine values were not different from baseline (P ≥ 0.5; Figure 1). The proportion of courses with increases of ≥3-fold of baseline at EOT was 13.5%, 15.6%, 5.7% and 8.5% for GOT, GPT, AP and BUN, and 7.1% and 1.4% for bilirubin and creatinine, respectively (Table 2). Increases in hepatic transaminase values appeared to correlate with the maximum daily dose (P < 0.01), and increases in bilirubin values with the cumulative dose (P < 0.005) of LAMB, respectively. For the remaining parameters, no correlation was found between dosage/duration of LAMB therapy and abnormal laboratory values.

With two exceptions, at least one additional nephrotoxic agent [cyclosporine A (CSA), tacrolimus, aminoglycosides or glycopeptides] was co-administered with LAMB; the number of nephrotoxic agents co-administered correlated with increased BUN and serum creatinine values at EOT (P = 0.0018 and P = 0.0602). Furthermore, there was a significant increase in the median serum creatinine value during courses with CSA (n = 44; P < 0.01) that was not observed in patients not receiving CSA. Similarly, median serum creatinine values at EOT were higher during courses with concomitant CSA as compared with values from courses without CSA administration (P < 0.01) [see Figure S1 available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Thirty-one of 32 courses of primary/secondary prophylaxis and 73/83 courses of empirical therapy were completed with success. In five courses (4.3%), treatment with LAMB was prematurely discontinued on the basis of grade III/IV treatment-related AEs; in four courses (3.5%), fungal breakthrough infections occurred [Candida albicans fungaemia (1), probable hepatosplenic candidiasis (1), possible invasive pulmonary aspergillosis (2)], and two patients died on treatment from refractory bacterial sepsis.

Among the seven courses with probable and proven invasive fungal infections, complete or partial responses were observed in two courses [probable invasive pulmonary Aspergillus fumigatus infection; acute lymphoblastic leukaemia (ALL) and allogeneic HSCT for refractory acute myeloblastic leukaemia (AML)]. Two further patients died with progressive probable A. fumigatus pulmonary and disseminated infection [allogeneic HSCT and graft versus host disease (GVHD)/graft failure], and all three patients with Candida bloodstream infections (refractory AML, refractory Ewing sarcoma, and graft failure post-allogeneic HSCT) died from refractory sepsis syndrome despite microbiological clearance of the bloodstream. Among the 19 courses administered for possible invasive pulmonary aspergillosis, four had a complete, twelve a partial, response; stable disease was observed in one course, and in two courses, treatment failed (progressive infiltrates; grade III treatment related AE).

Altogether, 122 of 141 treatment courses (87%) evaluated for assessment of efficacy responded to treatment, and 19 (13%) were considered treatment failures. Overall survival was 94% at EOT and 90% at 3 months post-EOT [see Table S3 available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. Overall response (86%), overall survival at EOT (93%) and at 3 months post-EOT (92%) during the first episode of LAMB treatment were similar when compared with the entire dataset [see Table S4 available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Discussion

Both pattern and extent of treatment-emergent AEs observed in this paediatric case series do not appear to be fundamentally different from those reported in prospective clinical trials in
Table 2. Increases in laboratory parameters during 141 courses of LAMB

<table>
<thead>
<tr>
<th>Parameter</th>
<th>≥1.5×BL at EOT, n (%)</th>
<th>≥2.0×BL at EOT, n (%)</th>
<th>≥3.0×BL at EOT, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>17 (12.0)</td>
<td>6 (4.3)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>40 (28.4)</td>
<td>33 (23.4)</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>30 (21.3)</td>
<td>22 (15.6)</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>Glutamate/oxalate transaminase</td>
<td>55 (39.0)</td>
<td>40 (28.4)</td>
<td>19 (13.5)</td>
</tr>
<tr>
<td>Glutamate/pyruvate transaminase</td>
<td>59 (41.8)</td>
<td>44 (31.2)</td>
<td>22 (15.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>48 (34.0)</td>
<td>25 (17.7)</td>
<td>8 (5.7)</td>
</tr>
</tbody>
</table>

LAMB, liposomal amphotericin B; BL, baseline; EOT, end of treatment.

adults and children. Despite a severely ill and heavily pretreated patient population, the rate of discontinuations due to drug-related AEs was <5% and compares favourably with the rates observed in these trials. While this low rate may not be surprising in a situation with limited alternative options—caspofungin being approved in October 2001 and voriconazole in March 2002, and paediatric dosing data available in 2002 and 2001, respectively—the low rates of more relevant changes in laboratory parameters of renal and hepatic function support the validity of this rate.

Clinical and laboratory AEs were frequent but mostly mild to moderate and only possibly related to the administration of LAMB. Of note, both occurrence and number of AEs correlated with cumulative exposure to LAMB and not with the maximum daily dose. Similar to the respective rates reported in prospective Phase II and III trials in paediatric patients, important class effects of amphotericin B of infusion-related reactions of fever, chills and rigor and relevant increases in either serum creatinine or BUN occurred in <10% of courses. No correlation was found between dosage or duration of LAMB and abnormal renal function parameters. However, the number of co-administered nephrotoxic drugs positively correlated with increased creatinine and BUN values at EOT, and median serum creatinine values at EOT were significantly higher in courses with CSA as compared with courses without CSA co-administration. This observation emphasizes the importance of concomitant nephrotoxic medications in the development of impaired renal function during treatment with LAMB. Electrolyte wasting, defined as any hypokalaemia or hypomagnesaemia or both, was common and observed in ~50% of patients; this was somewhat more frequent than observed in paediatric Phase II and III trials and may be related to differences in definitions and/or the use of ifosfamide and platinum derivatives.

Increases in serum bilirubin, alkaline phosphatase and hepatic transaminases may be observed in association with LAMB therapy. Approximately 15% and 7% of patients had increases in hepatic transaminases and serum bilirubin, respectively, at EOT to >3-fold the baseline value. While increases in bilirubin values correlated with exposure, increases in hepatic transaminases correlated with the maximum daily dose. In only one patient was LAMB discontinued due to hepatic AE. Overall, these data are similar to the increases in serum transaminase levels to ≥110 U/L in 17% and 23% and increases in serum bilirubin to ≥35 µmol/L in 11% and 12% of patients reported in children receiving empirical therapy with LAMB at 1 and 3 mg/kg/day.

Individual cases of substernal chest discomfort, respiratory distress and sharp flank pain have been noted during or following infusion of LAMB, and there have been observations of anaphylactic reactions to LAMB. Two patients had grade III/IV anaphylactic reactions that included flushing, nausea, vomiting, dyspnoea, drop in blood pressure and somnolence, and these occurred immediately after the start of the first and second dose, respectively. It is unclear whether this reaction is due to a component of the lipid carrier or to amphotericin B; however, similar reactions have been observed with amphotericin B deoxycholate and other lipid formulations. The occurrence of these reactions underscores the need for supervised infusion of the first doses of LAMB and caution against its use in the home-care setting.

Altogether, 122 of 144 treatment courses (87%) responded to treatment. Possible, probable or proven breakthrough infections occurred in 4/115 courses of primary/secondary prophylaxis or empirical therapy (3.5%). While 17/19 (89.5%) patients with possible pulmonary aspergillosis responded to treatment, outcome among the few patients with probable and proven fungal infections was poor with 5/7 patients dying with progressive disease. All five patients who failed therapy, however, were in terminal stages of their underlying condition. Considering the non-availability during the analysis of routine serum galactomannan testing, which is increasingly used to establish a diagnosis of probable invasive pulmonary aspergillosis, the severity of underlying conditions, the high number of patients post-allogeneic HSCT and of patients with prolonged granulocytopenia, these outcomes compare favourably with those reported from prospective clinical trials in adult and paediatric patients.

Although prospective, randomized trials are the gold standard for evidence, observational data can be useful in a variety of situations and provide generalizable data on effectiveness, safety and real-world treatment patterns. The results of this prospective observational analysis of 141 unselected, consecutive treatment courses in mostly granulocytopenic paediatric patients undergoing treatment for cancer or HSCT demonstrate acceptable safety and tolerance of LAMB in daily clinical practice without new safety signals, and effectiveness in prevention and treatment of invasive fungal infections.

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Liposomal amphotericin B in paediatric cancer patients

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Transparency declarations

A. H. G. has received research grants and has served as consultant and speaker to Gilead Sciences, Martinsried, Germany. All other authors: none to declare.

Supplementary data

Tables S1–S4 and Figure S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References