

1 **Original Article**

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3 **Efficacy and safety of low-dose liposomal amphotericin B in adult patients**
4 **undergoing unrelated cord blood transplantation**

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6 Running title: Low-dose liposomal amphotericin B in CBT

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25 **Abstract**

26 Liposomal amphotericin B (L-AMB) is widely used for empirical or preemptive
27 therapy and treatment of invasive fungal infection after cord blood
28 transplantation (CBT). We retrospectively examined the efficacy and safety of
29 low-dose L-AMB in 48 adult patients of CBT from between 2006 and 2017 in our
30 institute. Among the entire cohort, 42 (88%) patients received L-AMB as an
31 empirical or preemptive therapy. The median daily dose of L-AMB and the
32 median cumulative dose of L-AMB were 1.20 mg/kg/day (range, 0.62–2.60
33 mg/kg/day) and 30.6 mg/kg (range, 0.7–241.5 mg/kg), respectively. The median
34 duration of L-AMB administration was 21.5 days (range, 1–313 days).
35 Documented breakthrough fungal infection occurred in 1 patient during L-AMB
36 treatment, and 43 (90%) patients survived for at least 7 days after the end of
37 L-AMB treatment. Grade 3 or higher hypokalemia and hepatotoxicity were
38 frequently observed during L-AMB treatment. However, no patients developed
39 an increase in serum creatinine of grade 3 or higher. In the univariate analysis
40 using a logistic regression model, a duration of L-AMB treatment of more than 21
41 days and a cumulative dose of L-AMB more than 30 mg/kg were significantly
42 associated with nephrotoxicity and grade 3 hypokalemia. These data suggest
43 that low-dose L-AMB may be safe and effective in adult patients undergoing
44 CBT.

45

46 **Keywords:** liposomal amphotericin B, allogeneic hematopoietic cell
47 transplantation, cord blood transplantation, invasive fungal infection,
48 nephrotoxicity, hepatotoxicity

49 Introduction

50

51 Invasive fungal infections (IFIs) are a major cause of mortality and morbidity in
52 recipients of allogeneic hematopoietic cell transplantation (HCT). Although the
53 introduction of routine prophylactic use of antifungal drugs has decreased the
54 incidence of IFI and improved survival after allogeneic HCT [1], it caused
55 changes in the epidemiology of IFIs and the emergence of resistance against
56 triazoles and echinocandins [2]. Liposomal amphotericin B (L-AMB) has a wide
57 spectrum of activity against yeasts and molds including *Aspergillus* species and
58 Mucormycosis [3,4]. Previous prospective studies have demonstrated that
59 L-AMB is an effective empirical therapy for patients with persistent febrile
60 neutropenia despite the use of prophylactic antifungal agents and targeted
61 treatments of IFIs [5–8]. Although L-AMB has a significantly improved toxicity
62 profile compared with conventional amphotericin B deoxycholate (D-AMB),
63 adverse events such as hepatotoxicity, nephrotoxicity, electrolyte abnormalities,
64 and infusion-related reactions also frequently occurred for a recommended-daily
65 dose ranging between 3 and 6 mg/kg of L-AMB [3,4]. However, recent studies
66 have suggested that a low-dose of L-AMB (approximately less than 2
67 mg/kg/day) is effective and has a lower toxicity for patients with hematological
68 malignancies [9–14]. Therefore, the optimal daily dosage of L-AMB is
69 controvertible.

70 Cord blood transplantation (CBT) is an acceptable alternative to
71 unrelated allogeneic HCT for adult patients without human leukocyte antigen
72 (HLA)-matched related or unrelated donors [15–18]. However, the incidence of

73 infection is higher in CBT than HCT from other graft sources [19,20]. This is
74 probably due to prolonged neutropenia and delayed immune reconstitution,
75 which remain the disadvantages of CBT. Indeed, an Italian study demonstrated
76 that CBT was an independent risk factor for the development of IFI during the
77 early and mid-phases of HCT [2]. Moreover, potentially nephrotoxic drugs, such
78 as aminoglycosides, vancomycin, foscarnet, and calcineurin inhibitors, are
79 commonly used in CBT recipients and could induce nephrotoxicity and
80 electrolyte abnormalities along with the use of L-AMB. Based on these
81 backgrounds, L-AMB was intravenously administered at a dosage of less than 3
82 mg/kg/day in adult patients undergoing CBT in our institute. Therefore, we
83 retrospectively analyzed the efficacy and safety of low-dose L-AMB in patients
84 undergoing CBT.

85

86 **Patients and methods**

87

88 *Study patients and data collection*

89

90 This retrospective study included 48 adult patients who received low-dose
91 L-AMB during admission for single-unit unrelated CBT for hematological
92 malignancies at the Institute of Medical Science, The University of Tokyo
93 between January 2006 and December 2017. The indication of L-AMB for
94 empirical or preemptive therapy, the treatment of IFI, and the daily dose of
95 L-AMB were determined by the physicians. For patients who received a second
96 or more cycles of L-AMB treatment, only the first cycle of L-AMB treatment was

97 included in this study. The clinical data, which included the characteristics of
98 patients and transplantation, L-AMB treatment, laboratory parameters of renal
99 and hepatic function, electrolyte abnormalities during treatment, and
100 concomitant use of potential hepatotoxic and nephrotoxic drugs, were collected
101 from the medical records. The institutional review board of the Institute of
102 Medical Science, The University of Tokyo has approved this retrospective study.

103

104 *Endpoints and definitions*

105

106 The primary endpoints of this retrospective study were efficacy, safety, and
107 toxicity of low-dose L-AMB treatment during CBT.

108 Efficacy was assessed according to the five endpoints used in previous
109 reports [5–7]: (1) absence of any breakthrough fungal infection during therapy or
110 within seven days after the end of therapy; (2) successful treatment of any
111 baseline fungal infection; (3) survival for seven days after the end of therapy; (4)
112 no premature discontinuation of L-AMB treatment because of drug-related
113 toxicity or lack of efficacy; (5) resolution of fever, which was defined as a body
114 temperature below 38°C for at least 48 h, during neutropenia. Diagnosis of IFI
115 was based on the criteria of the European Organization for Research and
116 Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the
117 National Institute of Allergy and Infectious Disease Mycoses Study Group
118 (EORTC/MSG) [21].

119 Safety and toxicity were assessed according to the adverse events,
120 which were evaluated according to the National Cancer Institute-Common

121 Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.
122 Nephrotoxicity was defined as an increase in serum creatinine (Cre) of grade 2
123 or higher (i.e. an increase of 50% from baseline [22,23]). Pre-existing renal
124 dysfunction was defined as an estimated glomerular filtration rate less than 60
125 ml/min at the baseline within 48 h of the first L-AMB treatment.

126

127

128 *Statistical analysis*

129

130 Continuous variables were compared with the Kruskal–Wallis and Steel–Dwass
131 tests were used for multiple comparisons in the case of three groups. To identify
132 variables affecting each adverse event, a univariate analysis was performed
133 using a logistic regression model. The following variables were taken into
134 consideration: age (≥ 50 vs. < 50 years), sex (male vs. female), pre-existing renal
135 dysfunction (yes vs. no), duration of L-AMB treatment (≥ 21 vs. < 21 days),
136 median daily dose of L-AMB based on actual body weight (≥ 1.2 vs. < 1.2
137 mg/kg/day), cumulative dose of L-AMB based on actual body weight (≥ 30 vs.
138 < 30 mg/kg), cyclophosphamide in conditioning regimen (yes vs. no), busulfan in
139 conditioning regimen (yes vs. no), methotrexate in graft-versus-host disease
140 (GVHD) prophylaxis (yes vs. no), concomitant use of each drug, such as
141 aminoglycosides, vancomycin, foscarnet, calcineurin inhibitors, and
142 glucocorticoids (yes vs. no), and the number of potentially nephrotoxic drugs in
143 concomitant use (≥ 2 vs. < 2). For the univariate analysis to identify variables
144 affecting nephrotoxicity, 2 patients were excluded who developed an increase in

145 Cre probably due to multiple organ failure within 10 days before death. All
146 statistical analyses were performed in EZR (Saitama Medical Center, Jichi
147 Medical University, Saitama, Japan), a graphical user interface for R 3.0.2 (R
148 Foundation for Statistical Computing, Vienna, Austria) [24]. All *P*-values were
149 two-sided, and *P*-values<0.05 were considered as significant.

150

151 **Results**

152

153 *Characteristics of patients and transplantations*

154

155 The characteristics of patients and transplant procedures are summarized in
156 Table 1. The median age was 48 years (range, 17–68 years). 36 (75%) of the
157 patients were male, and the median body weight was 57.0 kg (range, 37.0–
158 105.5 kg). The most common disease type was acute myeloid leukemia (40%).
159 The myeloablative conditioning (MAC) regimen (88%) and methotrexate-based
160 GVHD prophylaxis (65%) were more commonly performed in this study group.
161 Among the MAC regimens, the most common conditioning regimen was total
162 body irradiation 12 Gy, cyclophosphamide, and cytosine arabinoside with or
163 without granulocyte colony-stimulating factor in patients with myeloid or
164 lymphoid malignancies, respectively [25–27].

165

166 *Treatment of L-AMB*

167

168 The characteristics of L-AMB treatment are summarized in Table 2. All patients

169 had received systemic antifungal drugs as prophylaxis with either voriconazole
170 (n=34), fluconazole (n=2), or micafungin (n=12) before switching to L-AMB.
171 Among the entire cohort, 42 (88%) patients received L-AMB for empirical or
172 preemptive therapy, and 6 (12%) patients received L-AMB for treatment of
173 probable or proven IFI. The median daily dose of L-AMB and the mean daily
174 dose of L-AMB based on the actual body weight were 1.20 mg/kg/day (range,
175 0.62–2.60 mg/kg/day) and 1.23 mg/kg/day (range, 0.62–2.47 mg/kg/day),
176 respectively. The median duration of L-AMB administration was 21.5 days
177 (range, 1–313 days). The median cumulative dose of L-AMB based on the
178 actual body weight was 30.6 mg/kg (range, 0.7–241.5 mg/kg). Twenty-three
179 patients started to receive L-AMB during neutropenia, which was defined as an
180 absolute neutrophil count of less than $0.5 \times 10^9/L$. Among them, 15 patients
181 received L-AMB as an empirical therapy for febrile neutropenia. During L-AMB
182 treatment, aminoglycosides, vancomycin, foscarnet, calcineurin inhibitors, and
183 glucocorticoids were concomitantly used in 9 (21%), 25 (58%), 14 (33%), 30
184 (70%), and 19 (44%) patients, respectively.

185

186 *Efficacy of L-AMB treatment*

187

188 The efficacies of L-AMB treatment after CBT are summarized in Table 3.
189 Documented breakthrough fungal infection occurred in 1 patient during L-AMB
190 treatment (fungemia due to *Fusarium*), indicating that the absence of
191 breakthrough fungal infection was observed in 47 (98%) of the 48 patients.
192 Among 6 evaluable patients who had a baseline fungal infection (proven

193 candidemia, n=2 and probable pulmonary aspergillosis, n=4), 4 (67%) patients
194 achieved successful treatment of IFI. Finally, 43 (90%) patients survived for at
195 least 7 days after the end of L-AMB treatment. Among the remaining 5 patients
196 who died, the causes of death were as follows: *Fusarium fungemia* (n=1),
197 candidemia (n=1), *Pneumocystis pneumonia* (n=1), multiple organ failure (n=1),
198 and relapse (n=1). Among the 43 patients survived for at least 7 days after the
199 end of L-AMB treatment, 17 (40%) patients prematurely discontinued L-AMB
200 treatment because of drug-related toxicity (n=14) or lack of efficacy (n=3).
201 Among 15 patients receiving L-AMB as an empirical therapy for febrile
202 neutropenia, 9 (60%) patients had resolution of fever during neutropenia.

203

204 *Safety and toxicity during L-AMB treatment*

205

206 The most common toxicities observed during L-AMB treatment were
207 infusion-related reactions, hepatotoxicity, nephrotoxicity, and electrolyte
208 abnormalities (Table 4).

209 Infusion-related reactions including skin eruption, nausea, dyspnea,
210 wheezing, fever, and muscle pain occurred immediately after the start of the first
211 infusion of L-AMB in 4 (8%) patients, which results in the discontinuation of
212 L-AMB.

213 As for hepatotoxicity, elevations of serum levels of aspartate amino
214 transaminase (AST), alanine amino transaminase (ALT), alkaline phosphatase
215 (ALP), and total-bilirubin (T-bil) during L-AMB treatment were frequently
216 observed, and grade 3 or higher elevations of AST, ALT, ALP, and T-bil were

217 observed in 4 (8%), 7 (15%), 2 (7%), and 13 (27%) patients, respectively (Table
218 3). Although there were significant differences of each level between AST, ALT,
219 ALP, and T-bil at baseline and those at the time of maximum elevation during
220 L-AMB treatment, serum levels of AST and T-bil at baseline were not
221 significantly different from each level at the end of L-AMB treatment (Figure 1).
222 In the univariate analysis using a logistic regression model, a duration of L-AMB
223 treatment of more than 21 days was significantly associated with grade 2 or
224 higher elevations of AST (hazard ratio [HR], 4.44; $P=0.04$) and ALP (HR, 4.44;
225 $P=0.04$).

226 Nephrotoxicity, which was defined as an increase in Cre of grade 2 or
227 higher, was observed in 12 (26%) patients. The median duration to development
228 of nephrotoxicity was 24.5 days (range, 2–127 days). Grade 3 hypokalemia was
229 observed in 11 (23%) patients. The median duration to development of
230 hypokalemia was 19 days (range, 3–83 days). Although grade 1
231 hypomagnesemia was observed in 23 (48%) patients, grade 2 or higher
232 hypomagnesemia was never observed during L-AMB treatment. Although there
233 were significant differences at each level between blood urea nitrogen (BUN),
234 Cre, potassium, and magnesium at baseline and at the time of maximum
235 elevation or minimum reduction during L-AMB treatment, serum levels of
236 potassium and magnesium at baseline were not significantly different from each
237 level at the end of L-AMB treatment (Figure 1). In the univariate analysis using a
238 logistic regression model, a duration of L-AMB treatment of more than 21 days
239 (HR, 20.20; $P=0.006$) and a cumulative dose of L-AMB of more than 30 mg/kg
240 (HR, 20.20; $P=0.006$) were significantly associated with nephrotoxicity. In

241 addition, a duration of L-AMB treatment of more than 21 days (HR, 5.91; $P=0.03$)
242 and a cumulative dose of L-AMB of more than 30 mg/kg (HR, 5.91; $P=0.03$)
243 were significantly associated with grade 3 hypokalemia.

244

245 *Survival after cessation of L-AMB treatment*

246

247 At 30 days after cessation of L-AMB treatment, 9 (19%) patients had died. The
248 primary causes of death were GVHD with or without organ failure in 5 patients,
249 fungemia (due to *Candida*, or *Fusarium*) in 2 patients, *Pneumocystis* pneumonia
250 in one patient, and underlying hematologic disease in one patient.

251

252 **Discussion**

253

254 The purpose of this single-center retrospective study was to evaluate the
255 efficacy and safety of low-dose L-AMB in adult patients undergoing CBT.
256 Although the majority of patients received L-AMB for empirical or preemptive
257 therapy during CBT, and the median daily dose of L-AMB was 1.20 mg/kg/day,
258 only one patient developed breakthrough fungal infection. In addition, grade 3 or
259 higher hypokalemia and hepatotoxicity, which were defined according to the
260 criteria of the NCI-CTCAE, were frequently observed. However, no patients
261 developed an increase in Cre of grade 3 or higher. These data indicated that
262 low-dose L-AMB may be safe and effective in adult patients undergoing CBT.

263 The optimal daily dose of L-AMB seems to be dependent on the types
264 of fungus infection and the strategy for L-AMB therapy. Daily doses ranging

265 between 3 mg/kg and 5 mg/kg of L-AMB have been recommended for the
266 treatment of invasive aspergillosis and candidiasis [8,28,29], whereas higher
267 doses of at least 5mg/kg of L-AMB could be more effective for the treatment of
268 *Cryptococcus meningitis* [30] and *Mucormycosis* [31,32]. However, Ellis et al.
269 reported a prospective randomized trial that compared the efficacy of two
270 dosages of L-AMB for treatment of invasive aspergillosis and found that a daily
271 dose of 1 mg/kg was as effective as that of 4 mg/kg [10]. Moreover, although the
272 optimal dose of L-AMB for empirical or preemptive therapy during neutropenia
273 remains unclear, several prospective and retrospective studies have suggested
274 that a daily dose as low as 1 mg/kg of L-AMB is effective for empirical therapy
275 and for prevention of IFI during neutropenia [9–14]. Among these studies,
276 Prentice et al. reported a prospective randomized trial that compared the
277 efficacy of two dosages of L-AMB and conventional D-AMB for empirical therapy
278 during neutropenia and found that a daily dose of 1 mg/kg of L-AMB could
279 provide an efficacy similar to that of 3 mg/kg of L-AMB [9]. Indeed, our study
280 showed that a median daily dose of 1.20 mg/kg of L-AMB provided favorable
281 results for the majority of empirical or preemptive antifungal therapies because
282 of the absence of breakthrough fungal infection and survival for at least 7 days
283 after the end of L-AMB treatment in adult patients undergoing CBT. These were
284 consistent with previous, larger studies with a daily dose of 3 mg/kg of L-AMB for
285 empirical therapy during neutropenia [5–7]. Moreover, the successful treatment
286 of base-line fungal infection in our study was also comparable with those in
287 previous studies [5,6], although only 6 patients were diagnosed with proven
288 (n=2) or probable (n=4) baseline IFI. Therefore, these data suggested that

289 low-dose L-AMB could be effective for empirical antifungal therapy, but further
290 studies are required to clarify the optimal dose of L-AMB for treatment of IFI in
291 adult patients undergoing CBT.

292 In our study, a higher incidence of hepatotoxicity was observed
293 compared with those in previous studies [5–7,22,33], which might be related to
294 differences in the definition of hepatotoxicity in each study. Nevertheless, the
295 cause of hepatotoxicity is likely to be multifactorial in allogeneic HCT. Therefore,
296 it was difficult to determine whether hepatotoxicity was due to the toxicity of
297 L-AMB or other complications following CBT, such as hepatic sinusoidal
298 obstruction syndrome, GVHD, infections, or concomitant use of other potentially
299 hepatotoxic drugs [34]. Moreover, our study demonstrated that hepatotoxicity
300 was not associated with a cumulative dose of L-AMB, which is consistent with a
301 previous study [22]. By contrast, although several potentially nephrotoxic drugs,
302 such as aminoglycosides, vancomycin, foscarnet, and calcineurin inhibitors, are
303 commonly used in patients undergoing CBT, our study showed that
304 nephrotoxicity was infrequently observed compared with previous studies
305 [5,6,22,35]. This lower nephrotoxicity in our study was the biggest advantage of
306 low-dose L-AMB treatment, although it might have been partly due to the fact
307 that several patients stopped L-AMB before the onset of nephrotoxicity.
308 Interestingly, our study demonstrated that nephrotoxicity was associated with a
309 cumulative dose of L-AMB, which is consistent with a previous study [22]. Based
310 on these data, hepatotoxicity appears to be dose-independent on the toxicity of
311 L-AMB, whereas nephrotoxicity appears to be dose-dependent on the toxicity of
312 L-AMB. These data suggested that the low-dose L-AMB contributed to the lower

313 rate of nephrotoxicity but not hepatotoxicity even after long-term use of L-AMB.

314 Our study had several limitations. First, this study was a retrospective
315 single-institute analysis. Therefore, the optimal daily dose of L-AMB for empirical
316 therapy and treatment of IFI after CBT requires further confirmation using
317 prospective, multicenter studies in the future. Second, all adverse events
318 possibly related to L-AMB are likely to be multifactorial after CBT, and a small
319 number of patients received low-dose L-AMB after CBT. Therefore, our results
320 might have been affected by a lower statistical power to detect the true effects.
321 Third, we were not able to use several novel triazole antifungal drugs, such as
322 posaconazole and isavuconazole, for prophylaxis and treatment of IFIs in this
323 study, because these drugs were not commercially available in Japan during this
324 study period. Although these novel drugs have an extended-spectrum activity
325 against yeasts and molds including not only *Aspergillus* species but also
326 Mucormycosis, the effect of these drugs on liver and renal function is usually
327 mild in the HCT setting [36,37]. Therefore, these novel triazole antifungal drugs
328 might be safe and effective in patients receiving CBT. Further studies are
329 required to optimize the antifungal strategy for patients receiving CBT.

330 In conclusion, our data demonstrated that low-dose L-AMB had no
331 inferior efficacy and a lower rate of nephrotoxicity for adult patients undergoing
332 CBT. Therefore, the relationship between the optimal daily dose of L-AMB and
333 efficacy or safety in CBT recipients should be investigated in future studies.

334

335 **Acknowledgements**

336

337 The authors thank all of the physicians and staff at the hospital in this study.

338

339 **Conflict of Interest**

340

341 The authors declare no competing financial interests.

342

343 **Funding**

344

345 S.T., and A.T. received research grants from Dainippon Sumitomo Pharma Co.,

346 Ltd. for research other than directory for this work. The other authors declare no

347 competing financial interests.

348

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546

547

548 **Figure 1.** Kinetics of hepatic and renal function parameters and electrolytes at
549 baseline, the maximum or minimum values during L-AMB treatment, and the
550 values at the end of therapy.

551

552 The line inside the box, the lower and upper box ends, and the lower and upper

553 whiskers represent the median value, the 25th and 75th percentiles, and the
554 10th and 90th percentiles of each value, respectively. The statistical differences
555 between each of the two groups among baseline, maximum or minimum values
556 during L-AMB, and at the end of therapy were analyzed by the Kruskal–Wallis
557 and Steel–Dwass tests.

558

559 * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, NS; not significant

560

561 AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline
562 phosphatase; T-bil, total-bilirubin; BUN, blood urea nitrogen; Cre, creatinine; K,
563 potassium; Mg, magnesium.

564

Table 1. Characteristics of the patients, cord blood units, and transplantations.

Characteristic	Value
Number of patients	48
Age at CBT, median (range), years	48 (17–68)
Body weight, median (range), kg	57.0 (37.0–105.5)
Sex	
Male	36 (75%)
Female	12 (25%)
Disease type	
AML	19 (40%)
ALL	8 (17%)
MDS	12 (25%)
CML	4 (8%)
NHL/ATL	4 (8%)
CAEBV	1 (2%)
Conditioning regimen	
MAC	42 (88%)
RIC	6 (13%)
Cyclophosphamide in conditioning regimen	33 (69%)
Busulfan in conditioning regimen	11 (23%)
GVHD prophylaxis	
CSP+MTX	31 (65%)
CSP+MMF	11 (23%)
CSP+PSL	1 (2%)
CSP	4 (8%)
TAC	1 (2%)

CBT, cord blood transplantation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; NHL, non-Hodgkin's lymphoma; ATL, adult T-cell leukemia-lymphoma; CAEBV, chronic active Epstein-Barr virus infection; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; GVHD, graft-versus-host disease; CSP, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; PSL, prednisolone; TAC, tacrolimus.

Table 2. Characteristics of liposomal amphotericin B treatment.

Characteristic	Value
Indication of L-AMB	
Empirical or preemptive therapy	42 (88%)
Treatment of probable or proven IFI	6 (12%)
Daily dose of L-AMB, mg/kg/day, median (range)	1.20 (0.62–2.60)
Duration of L-AMB treatment, days, median (range)	21.5 (1–313)
Cumulative dose of L-AMB, mg/kg, median (range)	30.6 (0.7–241.5)
Concomitant use of other drugs during L-AMB treatment	
Aminoglycoside	10 (21%)
Vancomycin	27 (56%)
Foscarnet	16 (33%)
Calcineurin inhibitors	33 (69%)
Glucocorticoids	21 (44%)
Number of nephrotoxic drugs in concomitant use	
0	4 (8%)
1	10 (21%)
2	29 (60%)
3	2 (4%)
4	3 (6%)

Table 3. Efficacy of low-dose L-AMB after CBT.

Response indicator	Number of patients
No breakthrough fungal infection	47/48 (98%)
Successful treatment of base-line fungal infection	4/6 (67%)
Survival for at least 7 days after the end of treatment	43/48 (90%)
No discontinuation due to toxicity or lack of efficacy	26/43 (60%)
Resolution of fever during neutropenia	9/15 (60%)

Table 4. Toxicity of low-dose L-AMB after CBT.

	Grade 1	Grade 2	Grade 3	Grade 4	Total
AST	20 (42%)	5 (10%)	4 (8%)	0	29 (60%)
ALT	20 (42%)	5 (10%)	7 (15%)	0	32 (67%)
ALP	23 (48%)	11 (23%)	2 (4%)	0	36 (75%)
T-bilirubin	10 (21%)	4 (8%)	7 (15%)	4 (8%)	25 (52%)
Serum creatinine	27 (56%)	12 (25%)	0	0	39 (81%)
Hypokalemia	4 (8%)	19 (40%)	11 (23%)	0	34 (71%)
Hypomagnesemia	23 (48%)	0	0	0	23 (48%)

Toxicities were evaluated according to NCI-CTCAE version 4.0.

Figure 1

