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CLINICAL THERAPEUTICS

Retrospective Cohort Analysis of Liposomal Amphotericin B Nephrotoxicity in Patients with Hematological Malignancies

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ABSTRACT We retrospectively examined the incidence, onset, risk factors, and outcomes of renal injury during 103 treatment courses of liposomal amphotericin B (L-AMB) in 97 adult patients with hematological malignancies. All the patients were analyzed before, during, and after the administration of L-AMB, and renal injury was graded according to the RIFLE criteria (risk, injury, failure, loss of function, end-stage renal disease). Most patients (87.3%) received L-AMB at 3 mg/kg of body weight/day. Nearly two-thirds (61.7%) of the treatment courses did not meet any RIFLE category for renal injury, while 19.4% of patients were classified at risk, 13.6% met an injury classification, and 5.8% were categorized as developing renal failure. However, 15% of the patients developed renal injury within 48 h of the onset of multiorgan failure associated with sepsis, bleeding, or progressing malignancy. When these patients were analyzed as a competing risk for L-AMB-associated renal injury (RIFLE category I or above) in a multivariate Cox regression model, receipt of cyclosporine (subhazard ratio [SHR], 2.62; 95% confidence interval [CI], 1.10 to 6.27; $P = 0.03$), cyclosporine plus furosemide at ≥40 mg/day (SHR, 5.46; 95% CI, 1.89 to 15.74; $P = 0.002$), or cyclosporine plus foscarnet (SHR, 9.03; 95% CI, 3.68 to 22.14; $P < 0.0001$) were the only comedications significantly associated with increased rates of renal injury. The cumulative incidence of L-AMB renal injury during the first 10 days of therapy was 7% overall but only 3% in patients who were not receiving cyclosporine. Hence, the renal risk of L-AMB therapy may be lessened if patients are switched to alternative agents after 7 to 10 days or if aggressive diuresis and/or foscarnet is avoided, especially among patients receiving calcineurin inhibitors.

KEYWORDS liposomal amphotericin B, nephrotoxicity, RIFLE, hematological malignancy, RIFLE criteria

Nephrotoxicity is the main treatment-limiting adverse effect of liposomal amphotericin B (L-AMB), but the risk varies depending on the patient population, daily administered dose, duration of therapy, and receipt of concurrent nephrotoxic agents (1). Most studies that have examined the incidence and risk factors for L-AMB nephrotoxicity were published during the 1990s and early 2000s and do not reflect contemporary treatment strategies for invasive fungal disease. For example, it is now uncommon to start treatment with amphotericin B-deoxycholate in patients with hematological malignancies and then switch to L-AMB after a patient develops renal injury—a strategy that was widespread in the 1990s but was later shown to be inferior to voriconazole for the treatment of invasive aspergillosis (2). Clinicians also now have

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more alternatives for switching therapy in patients with early evidence of renal impairment.

Changes in the management of hematological malignancies over the last 2 decades may also impact the risk for L-AMB renal injury. During the 1990s, patients with relapsing hematological malignancies often received several courses of salvage chemotherapy before progressing to myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) (3). Currently, eligible patients are more likely to receive targeted therapies or undergo allogeneic HSCT after their first complete remission with lower (nonmyeloablative) doses of conditioning chemotherapy, which is associated with less organ toxicity (4).

Hence, the incidence and outcomes of L-AMB-associated renal injury have likely changed over the last 2 decades. Comparisons of older literature on L-AMB-associated renal injury to that of the current era are complicated by the frequent use of nonstandardized definitions for renal toxicity (5, 6), heterogeneous patient populations (7, 8), consideration of different amphotericin B formulations as a single drug (9), or failure to differentiate L-AMB renal injury from renal failure that develops as part of multiorgan failure syndrome or sepsis associated with terminal leukemia.

The goal of this study was to define the contemporary incidence, outcomes, and risk factors for L-AMB-associated renal injury in patients undergoing treatment for hematological malignancies. We hypothesized that the incidence of L-AMB renal injury, defined as patients who met the "I" criteria in the validated RIFLE criteria (risk, injury, failure, loss of function, end-stage renal disease) (10), would occur in less than 10% of patients during the first 10 days of therapy and would be even less frequent in patients who were not receiving concurrent nephrotoxic therapies.

RESULTS

Study subjects. We identified 115 L-AMB treatment courses in 97 patients from 2007 to 2014. Twelve cases (10.4%) were excluded from the analysis because the patient had received low (1 mg/kg of body weight/day) or infrequent (10 mg/kg once weekly) L-AMB dosing for prophylaxis. Among the 103 treatment courses analyzed, two-thirds (63/103; 61.2%) did not meet any RIFLE criteria during L-AMB therapy. In the remaining 40 (38.8%) treatment courses that met the RIFLE criteria, no patients progressed to loss of renal function or end-stage renal disease ("L" and "E" categories, respectively). One patient received hemodialysis at the time of L-AMB treatment and exhibited persistently decreasing serum creatinine (SeCr) concentrations for the duration of therapy.

The baseline characteristics of patients who met any of the RIFLE criteria for renal injury during L-AMB treatment were similar to those of patients without evidence of renal injury (Table 1). No significant differences were detected in terms of baseline comorbidity at the time of L-AMB treatment, liver disease, history of diabetes, or the need for intensive care unit (ICU) care during L-AMB treatment. Rates of preexisting renal disease were similar in the two groups (2.5% versus 1.6%; $P = 0.99$). However, patients who had undergone allogeneic HSCT were more likely to meet RIFLE injury criteria than patients without transplants (47.5% versus 28.6%; $P = 0.002$). The distributions of European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) diagnosis categories and or culture-documented pathogens (less than 20% of cases) were also similar in the two groups.

In univariate analysis, no differences in overall mortality, outcome of invasive fungal disease, or duration of hospitalization was associated with meeting RIFLE criteria during L-AMB treatment (Table 1).

RIFLE criteria incidence and outcomes. The incidences of the highest degree of renal injury graded according to the RIFLE criteria during L-AMB therapy, at the completion of therapy, and at 7 days following completion of therapy are presented in Fig. 1. Among the 38.9% of patients who met any of the RIFLE injury criteria during L-AMB treatment, 19.4% of the treatment courses were associated with the "risk" of renal injury, 13.6% of cases were associated with renal "injury," and 5.8% of cases were

TABLE 1 Baseline patient characteristics

Variable	Value for patients who:		
	Did not meet RIFLE criteria (n = 63)	Met RIFLE criteria (n = 40)	P value
Age (yr) [median (IQR)]	50 (42–61)	44 (34–57)	0.66
Sex (male) [no. (%)]	32 (50.8)	19 (48.8)	0.84
Hematological disease [no. (%)]			
Acute myelogenous leukemia/ myelodysplastic syndrome	40 (63.5)	22 (55.0)	0.07
Acute lymphocytic leukemia	8 (12.7)	9 (22.5)	0.13
Lymphoma	7 (11.1)	9 (22.5)	0.16
Chronic myeloproliferative syndrome	4 (6.3)	1 (2.5)	0.65
Chronic lymphocytic leukemia	1 (1.6)	1 (2.5)	0.99
Myeloma	3 (4.8)	1 (2.5)	1.00
Aplastic anemia	0 (0)	1 (2.5)	0.39
Disease status [no. (%)]			
Complete remission	21 (33.3)	18 (45.0)	0.30
At initial diagnosis	12 (19.0)	7 (17.5)	0.99
Relapse/progression	30 (47.6)	15 (37.5)	0.21
Treatment [no. (%)]			
Induction chemotherapy	23 (36.5)	11 (27.5)	0.39
Consolidation chemotherapy	8 (12.7)	1 (2.5)	0.15
Autologous HSCT	5 (7.9)	1 (2.2)	0.40
Allogeneic HSCT	18 (28.6)	24 (47.5)	0.06
No chemotherapy	8 (12.7)	8 (20.0)	0.41
Experimental (targeted) therapy	1 (1.6)	0 (0)	0.99
Neutropenia [no. (%)]	59 (93.6)	41 (91.9)	0.40
Corticosteroids [no. (%)]	16 (25.4)	17 (42.5)	0.09
Charlson comorbidity index [median (IQR)]	4 (2–5)	4 (2–5)	0.97
Diabetes [no. (%)]	7 (11.1)	5 (12.5)	0.99
Preexisting renal disease [no. (%)]	1 (1.6)	1 (2.5)	0.99
Hepatic disease [no. (%)]	2 (3.2)	1 (2.5)	0.99
Required ICU care [no. (%)]	7 (11.1)	2 (5.0)	0.31
Prophylaxis [no. (%)]			
Nystatin (nonabsorbable)	7 (11.1)	2 (5.0)	0.47
Itraconazole	7 (11.1)	2 (5.0)	0.47
Fluconazole	27 (42.9)	25 (62.5)	0.07
Posaconazole	8 (12.7)	3 (7.5)	0.52
Voriconazole	2 (3.2)	1 (2.5)	0.99
L-AMB	7 (11.1)	3 (7.5)	0.73
Caspofungin	0 (0)	3 (7.5)	0.06
None	5 (7.9)	1 (2.5)	0.40
Indications [no. (%)]			
Possible fungal infection	22 (34.9)	19 (47.5)	0.22
Probable fungal infection	23 (36.5)	11 (27.5)	0.39
Proven fungal infection	8 (12.7)	4 (10.0)	0.76
Preemptive [no. (%)]	8 (12.7)	4 (10.0)	0.76
Empirical therapy [no. (%)]	2 (3.2)	2 (5.0)	0.64
IFI culture documented [no. (%)]			
Aspergillus spp.	10 (15.9)	3 (7.5)	0.34
Candida spp.	2 (3.2)	1 (2.5)	0.66
Blastoschizomyces spp.	0 (0)	1 (2.5)	0.21
No culture documentation	51 (81.0)	35 (87.5)	0.43
Outcome [no. (%)]			
Discharged without antifungal	17 (27.0)	13 (32.5)	0.66
Discharged with antifungal	29 (46.0)	15 (37.5)	0.41
Died with invasive fungal infection	11 (17.5)	9 (22.5)	0.53
Death from other cause	1 (1.6)	1 (2.5)	0.99
No. of hospitalization days [median (IQR)]	42 (33.5–64.5)	43.5 (26–61)	0.61

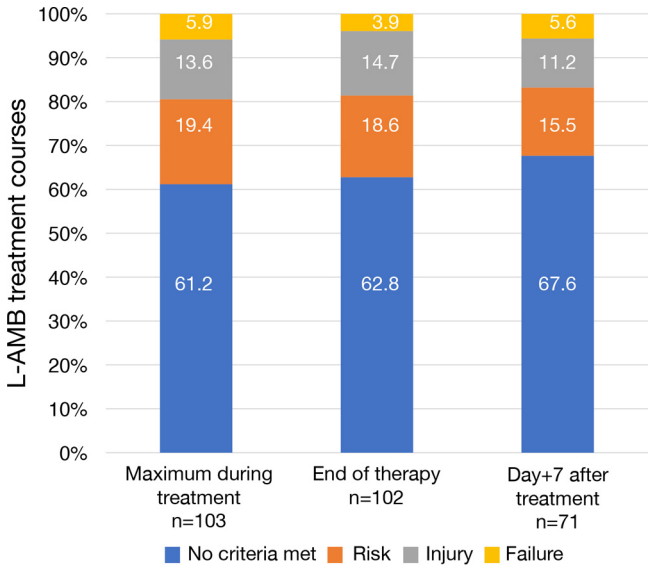

FIG 1 Incidence of renal risk, injury, or failure among patients with hematological malignancies treated with L-AMB.

associated with "failure." The percentages of patients in each RIFLE category were similar at the end of and 1 week following L-AMB treatment. No significant trend of increased mortality was evident for patients who met the risk or injury category (data not shown). However, the 30-day all-cause mortality rate was nearly 5 times higher in patients who developed renal failure (relative risk [RR], 4.55; 95% confidence interval [CI], 1.73 to 11.91; $P = 0.0007$). All 6 patients who developed renal failure also had evidence of multiorgan failure associated with sepsis, hemorrhage, and refractory underlying hematological malignancy. Only one of the six patients with renal failure (20%) was alive at 30 days.

L-AMB treatment risk factors for nephrotoxicity. Details concerning L-AMB treatment regimens and adverse effects are presented in Table 2. The distributions of daily AMB doses (milligrams per kilogram) were similar between patients who met RIFLE criteria for injury and those without injury. The median duration of L-AMB therapy was significantly longer in patients who developed evidence of renal injury (median, 8 versus 13 days; $P = 0.009$).

Competing risks for L-AMB-associated renal injury. Three of the 20 patients (15%) met the injury classification criteria only within 48 h of developing multiorgan failure with sepsis and/or hemorrhage and were therefore categorized as having a competing risk for L-AMB renal injury. Therefore, in the exploratory analysis of concomitant drug risk factors for renal injury, 83 patients were coded as not developing injury, 17 patients as developing L-AMB-associated renal injury, and 3 treatment episodes as non-LAMB-associated acute renal injury or failure.

Concomitant nephrotoxic medications. Cyclosporine, teicoplanin, foscarnet, and high-dose furosemide were the most common medications associated with the development of renal injury by univariate analysis during L-AMB therapy (Fig. 2). When these drugs were analyzed in a multivariate Cox regression competing-risk model, only the receipt of cyclosporine alone (subhazard ratio [SHR], 2.62; 95% CI, 1.10 to 6.27; $P = 0.03$) or in combination with furosemide (≥40 mg/day) (SHR, 5.46; 95% CI, 1.89 to 15.74; $P = 0.002$) or foscarnet (SHR, 9.03; 95% CI, 3.68 to 22.14; $P < 0.0001$) resulted in significantly higher SHR for renal injury. A plot of the predicted cumulative incidence function for renal injury or failure stratified by receipt of cyclosporine alone or in combination with high-dose furosemide or foscarnet is shown in Fig. 3.

Overall, concomitant cyclosporine therapy was associated with a nearly 3-fold-higher 30-day incidence of renal injury during L-AMB therapy (incidence rate ratio [IRR],

TABLE 2 L-AMB adverse effects and risk factors

Variable	Value for patients who:		*P* value
	Did not meet RIFLE criteria ($n = 63$)	Met RIFLE criteria ($n = 40$)	
L-AMB dose administered [no. (%)]			
3 mg/kg/day	55 (87.3)	32 (80.0)	0.40
5 mg/kg/day	3 (4.8)	1 (2.5)	0.99
5 mg/kg/day to 3 mg/kg/day	3 (4.8)	1 (2.5)	0.99
Days of L-AMB [median (IQR)]	8 (4–16)	13 (9–18)	0.009
Infusion reaction [no. (%)]			
None	59 (93.7)	38 (95.0)	0.99
Cough	1 (1.6)	0 (0)	1.00
Cough plus dyspnea	1 (1.6)	0 (0)	1.00
Cough, vomiting, dyspnea	1 (1.6)	0 (0)	1.00
Rash	0 (0.0)	1 (2.5)	0.39
Back pain	1 (1.6)	1 (2.5)	0.99
SeCr (mg/dl) [median (IQR)]			
Baseline	0.59 (0.46–0.74)	0.46 (0.40–0.61)	0.32
Highest	0.64 (0.53–0.85)	1.17 (0.72–1.41)	<0.0001
End of therapy	0.68 (0.48–0.99)	0.97 (0.26–1.41)	0.32
Wk after completion	0.70 (0.51–1.11)	1.1 (0.82–1.32)	0.40
Serum potassium (meq/liter) [median (IQR)]			
Baseline	4.0 (3.6–4.2)	3.9 (3.7–4.3)	0.74
Lowest	3.5 (3.1–4.2)	3.1 (2.8–3.3)	0.07
End of therapy	3.7 (3.4–4.5)	3.8 (3.3–4.2)	0.98
Wk after completion	3.8 (3.4–4.1)	4.2 (3.7–4.5)	0.04
Mean urine output [ml/kg · hr (±SD)]			
Baseline	0.02 (±0.15)	0.03 (±0.16)	0.21
Highest	0.10 (±0.30)	0.40 (±0.59)	<0.0001
End of therapy	0.02 (±0.15)	0.09 (±0.38)	0.08
Wk after completion	0.02 (±0.15)	0.04 (±0.19)	0.75

2.71; 95% CI, 1.05 to 7.78; $P = 0.01$). Cyclosporine plus furosemide increased the risk of renal injury 4-fold (IRR, 4.20; 95% CI, 1.54 to 10.54; $P = 0.0016$), while concomitant cyclosporine and foscarnet increased the risk 5-fold (IRR, 4.98; 95% CI, 1.02 to 16.70; $P = 0.016$).

DISCUSSION

The main finding of this study was that approximately one-third of patients with hematological malignancies receiving L-AMB treatment experienced changes in renal function that was associated with risk (19.4%) of renal injury, injury (13.6%), or renal failure (5.8%). However, renal failure occurred only in patients with multiorgan failure associated with terminal stages of leukemia.

Another finding of our study was that the incidence of renal injury overall (i.e., patients reaching the category of I or above, that is, equivalent to ≥2× baseline serum creatinine) was low during the first 7 to 10 days of therapy. However, this window of low risk during L-AMB treatment was affected by concomitant medications, particularly calcineurin inhibitors alone or in combination with diuretic therapy or foscarnet. The time to reach a 5% cumulative incidence of renal injury during L-AMB treatment in patients not receiving cyclosporine was approximately 12 days. In patients receiving cyclosporine, this window was reduced to 9 days, but it was less than 5 days if the patients also received furosemide or foscarnet.

Other nephrotoxic therapies or intravenous contrast did not emerge as independent risk factors for accelerating L-AMB renal injury. Amikacin was administered to 22 to 30% of the patients, but our standard practice is to discontinue empirical aminoglycosides included in antibiotic regimens for febrile neutropenia after 3 to 5 days once a patient

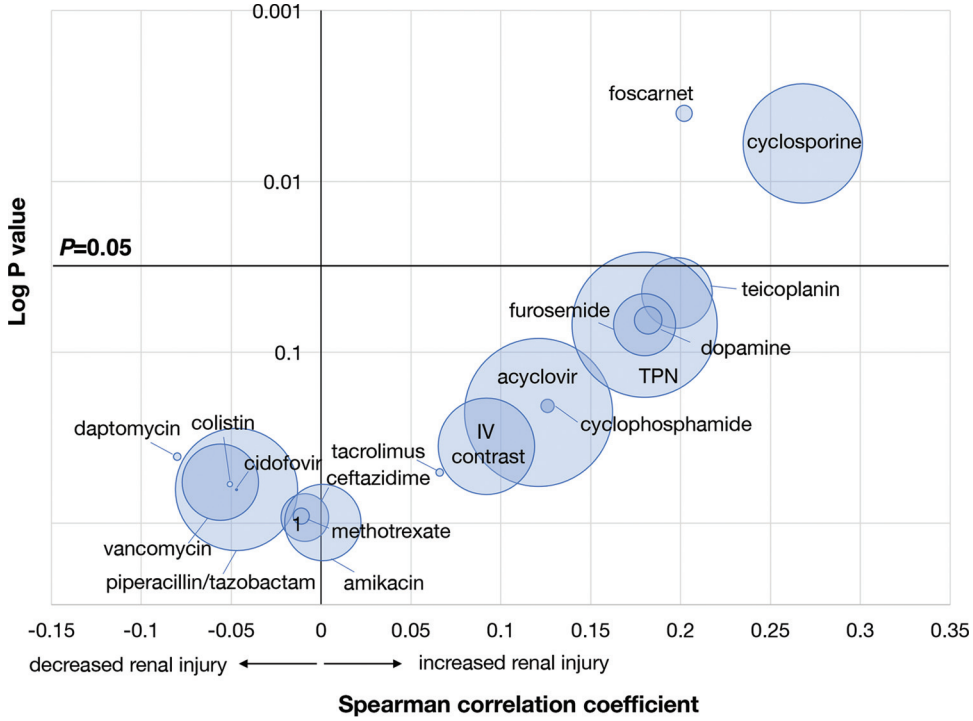

FIG 2 Spearman rank correlation of comedication use with observed renal injury in patients treated with L-AMB. The *x* axis represents negative (left) or positive (right) correlation coefficients for renal injury, defined as a RIFLE injury (I) category or higher. The *y* axis is the $\log_{10}$ *P* value of the correlation coefficient. The sizes of the bubbles reflect the prevalence of the specific comedication use in the study population, with larger bubbles representing higher numbers. TPN, total parenteral nutrition.

has documented negative blood cultures unless isolates display higher MICs or resistance to beta-lactam or carbapenem antibiotics (11). Similarly, the nephrotoxic impact of vancomycin may have been reduced in our analysis because of a relatively low frequency of *Staphylococcus aureus* bloodstream infections in our institute (tunneled catheters are rarely used) and the more frequent use of teicoplanin or daptomycin in higher-risk patients to avoid additive nephrotoxicity. This likely explains the correlation

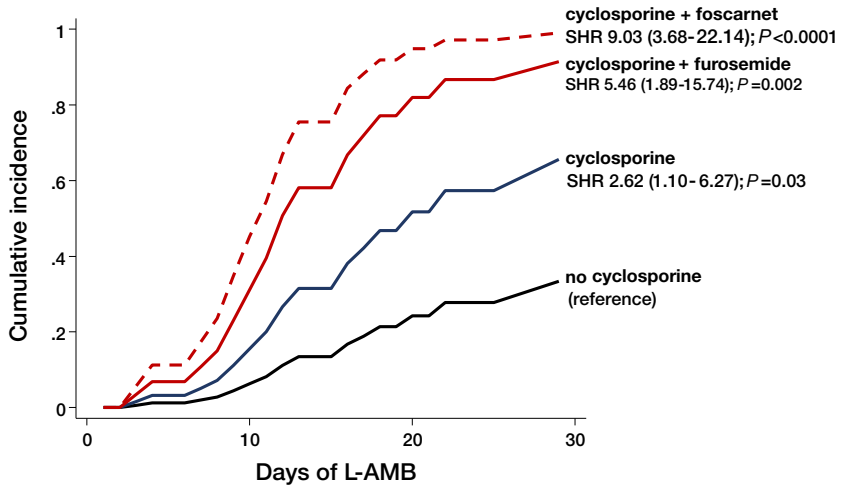

FIG 3 Cumulative incidence of renal injury or failure associated with L-AMB treatment estimated by competing-risk Cox regression (Fine and Gray model). The strength of the association between each predictor variable and renal injury or failure was assessed using the SHR, which is the ratio of hazards associated with the cumulative incidence function (CIF) in the presence and in the absence of concomitant cyclosporine, furosemide, or foscarnet. The numbers in parentheses are the 95% CI.

of teicoplanin use with renal injury in the univariate analysis. We also have institutional protocols for avoidance of intravenous contrast in patients at high risk for renal injury, even though a recent propensity-score-adjusted analysis suggested that intravenous contrast does not increase the risk for L-AMB kidney injury (12). However, calcineurin inhibitors are an essential component of the posttransplant immunosuppression protocols and cannot be interrupted during L-AMB treatment. Therefore, it is not surprising that cyclosporine emerged as the foremost drug for augmenting the rate of renal injury during L-AMB therapy.

Published studies on nephrotoxicity risks with L-AMB vary depending on the patient population and the definitions used to classify renal injury. Clinical trials that utilized a definition of doubling of baseline serum creatinine have reported rates of renal injury ranging from 9.4% to 18.7% with L-AMB therapy (13–15). A multicenter prospective observational study of amphotericin B-associated nephrotoxicity in 20 European hematology wards from 2000 to 2002 (7) found that among the cohort of patients treated with L-AMB ($n = 112$), 69.3% did not experience worsening renal function, 21.8% developed modest renal injury (≥50% increase in peak creatinine levels), 5.9% developed moderate renal injury (100 to 199% increase in peak serum creatinine), and 3% developed a severe renal injury (≥200% increase in peak serum creatinine). Similar to our study, the investigators found that duration of treatment and receipt of immunosuppressive medications, but not specific chemotherapy or aminoglycosides, were risk factors for nephrotoxicity during L-AMB treatment. The investigators also reported that, similar to our results, severe renal injury was associated with an approximately 5-fold-higher probability of death (7). However, the investigators did not attempt to differentiate patients who developed renal failure as part of a multiorgan failure syndrome associated with sepsis or malignancy. Moreover, they did not explore the incidence of renal injury at different time periods or its reversibility. Unlike our study, the authors reported that mild nephrotoxicity was associated with increased hospital length of stay, although this analysis was not specifically presented for L-AMB-treated patients, who accounted for only 27% of the investigated regimens (most patients [62%] received amphotericin B-deoxycholate).

Two retrospective Brazilian studies have also examined the incidence of L-AMB nephrotoxicity in mixed patient populations using either the RIFLE criteria (8) or the more sensitive Kidney Disease Improving Global Outcome (KIDGO) staging criteria (16). Of the two, the study by Falci et al. (8) is more applicable to our analysis, as they included 105 patients treated with L-AMB and found 22% of the patients fell into the risk category, 3.7% progressed to injury, and 2.4% developed failure. However, after 3 months, 88% of the patients did not exhibit any signs of injury, and 12% remained in the risk category only.

Our study has several limitations. Because it is an analysis from a single center, the incidence of renal injury during L-AMB treatment is influenced by the study population mix and supportive care approaches used in our institution. The number of treatment courses included in our analysis from a 7-year period (2007 to 2014) may also limit the power of the study to detect less common risk factors for L-AMB renal injury. Nevertheless, our findings are consistent with previous studies but define an initial treatment window for use of L-AMB when nephrotoxicity risk is low. We also show how the most common concomitant nephrotoxic therapies impact this safety window and try to account for a confounding bias of terminal events associated with uncontrolled malignancy that lead to severe renal injury or failure.

L-AMB is primarily administered at the lowest licensed dose of 3 mg/kg/day for empirical therapy of invasive fungal disease. Centers where L-AMB is routinely administered at higher doses (i.e., 5 to 7.5 mg/kg/day), which is not advocated by current FDA- and European Medicine Agency-approved labeling, may observe a higher incidence of nephrotoxicity. Recent clinical studies have suggested limited benefits and higher risk of nephrotoxicity with increasing daily doses of L-AMB in the treatment of cryptococcal meningitis (17), invasive aspergillosis (18), and possibly mucormycosis (19). However, novel dosing approaches using a combination of high induction doses

followed by lower maintenance doses are under investigation for cryptococcosis (20, 21).

Finally, we did not compare outcomes to a matched cohort of patients with hematological diseases treated with triazoles or echinocandins. A case-cohort study design of this type could provide further insight into possible excess length of hospital stay, resource utilization, or mortality associated with L-AMB-associated renal injury.

In conclusion, we found that in a contemporary population of patients with hematological malignancies, L-AMB treatment at primarily 3 mg/kg/day is associated with a low risk of renal injury during the first 10 days of therapy that is accelerated by cyclosporine, especially if the patient receives furosemide and/or foscarnet. Therefore, the renal risks of empirical L-AMB therapy may be reduced if patients are switched to alternative therapies after 7 to 10 days of treatment and aggressive diuresis or foscarnet is avoided, especially in patients who require calcineurin inhibitors during L-AMB treatment.

MATERIALS AND METHODS

Study setting. A retrospective cohort analysis of all the patients admitted to our hematology institute (Lorenzo e Ariosto Seràgnoli Institute of Hematology, Policlinico S. Orsola-Malpighi, University of Bologna, Bologna, Italy) who received treatment with L-AMB from 2007 to 2014 was performed. Patients were identified from pharmacy records and an established prospective hematology infection database approved by the institutional ethics committee. The patients provided informed consent on the first day of their hospitalization for inclusion in the database.

Study subjects. All adult patients (>18 years) between 2007 and 2014 were included in the study if they had received at least one intravenous dose of L-AMB. For patients with multiple admissions, each admission episode with a unique L-AMB treatment course was included as a new case.

Data source and collection. Clinical and laboratory data were extracted from patient medical records and registered on a standardized electronic collection form. Data were collected 1 month prior to, during, and up to 90 days following L-AMB completion, hospital discharge, or patient death. We recorded patient demographics; hematological disease diagnosis, status, and treatment; history of autologous or allogeneic HSCT; Charlson comorbidity index; clinical history of preexisting renal disease (history of nephropathy or baseline SeCr of >1.5 mg/dl); diabetes; hepatic disease (clinically or histologically documented); neutropenia (absolute neutrophil count of <500 cells/mm^3); receipt of corticosteroids (0.5 mg/kg/day prednisone equivalent for ≥14 days in the previous month); and need for ICU admission. We also documented prior antifungal treatment or prophylaxis, the indication for antifungal therapy, and the category of invasive fungal disease diagnosis according to EORTC/MSG definitions (22). The daily L-AMB dose and duration of therapy were recorded, along with outcome measures, including overall 30-day mortality, death with active fungal disease, discharge with or without antifungal therapy, and duration of patient hospitalization.

Nephrotoxicity risk. We classified patients' risk or stage of renal impairment according to their maximal RIFLE criteria (10) 24 h before L-AMB administration, every 72 h during therapy, at the end of therapy, and 7 days following completion of therapy. Patients (i) with a serum creatinine increase of 1.5 to 2 times baseline or decrease in urine output of 0.5 ml/kg/h for <6 h were classified as at risk, (ii) with a serum creatinine increase of 2 to 3 times baseline or urine output decrease of 0.5 ml/kg/h for 12 h were categorized as having injury, (iii) with a serum creatinine increase greater 3 times baseline or urine output less than 0.3 ml/kg/h for 24 h were classified as experiencing failure, (iv) with a complete loss of kidney function for greater than 4 weeks requiring dialysis were classified as experiencing loss, and (v) with complete loss of kidney function for more than 3 months requiring dialysis were classified as having end-stage renal disease.

Serum potassium concentrations were also documented, with hypokalemia defined as a serum K^+ level of <3.2 meq/liter. We documented recent (within 30 days) and concomitant use of nephrotoxic drugs. Patients routinely received hydration (250 to 500 ml 0.9% NaCl) before and after L-AMB infusions and were managed with a standardized electrolyte replacement protocol for potassium replacement (goal, K^+ at 4.0 meq/liter) and magnesium supplementation (5 g of $MgSO_4$ intravenously [i.v.] daily until serum K^+ levels normalized; thereafter, oral Mg^{2+} supplementation was used at a daily dose of 535 mg [5.33 meq] MgCl twice daily).

Statistical analysis. The primary objective of this study was to define the periodic and cumulative incidence of renal injury associated with L-AMB treatment in patients with hematological malignancies. To meet this objective, the sample size was calculated based on a 22% (±5%) incidence of patients meeting the risk category criterion during L-AMB therapy, as described by Falci et al. (8). A sample size of at least 100 patients provided 95% confidence that the true incidence of patients falling in the risk category of the RIFLE criteria would be between 17 and 27%. Patients with missing data (1% of reviewed cases) were excluded from the analysis. The relationship of the highest RIFLE criterion achieved by each patient during hospitalization and 90-day all-cause mortality was analyzed by the Kaplan-Meier method.

Secondary objectives of this study were to identify concomitant drug therapies associated with increased 30-day incidence of renal injury, failure, or loss (RIFLE category I or above) during L-AMB treatment. To perform this analysis, we first compared demographic, underlying disease, and treatment

risk factors for patients who met the criteria for risk categorization. Continuous data were summarized by median (interquartile range) and compared by using the Wilcoxon method or Student's *t* test. Dichotomous variables were compared using Fisher's exact test or the chi-square test. The correlation of concomitant medications and renal injury was analyzed using the Spearman rank test and visualized using a weighted bubble plot.

Medications identified in the univariate analysis with a *P* value of <0.1 were introduced stepwise into the Cox regression model of competing risk for renal injury (Fine and Gray model) for calculation of the SHR (23). This model allowed the simultaneous estimation of two independent competing events: L-AMB-associated renal injury or failure versus renal injury associated with a terminal malignancy. Specifically, patients were considered a competing event if they developed renal injury or failure only within 48 h of a multiorgan failure syndrome or death associated with sepsis, bleeding, or uncontrolled malignancy. The proportional-hazards assumption and goodness of fit of the final regression model were assessed using methods described by Zhou et al. (24). All statistical analysis was performed using Stata IC version 13.1 (Stata Corp., College Station, TX).

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M.S. developed the project, collected data, and wrote the first draft of the manuscript. N.V. and M.C. reviewed cases and revised the manuscript. A.M. collected data on nephrotoxicity indicators, and M.M. extracted and analyzed pharmacy data. R.E.L. performed the data analysis and revised the manuscript.

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