Medicina Intensiva 49 (2025) 50–56

medicina intensiva

http://www.medintensiva.org/

SCIENTIFIC LETTERS

Clinical experience on the use of liposomal amphotericin B in the ICU

Liposomal amphotericin B in ICU

Dear Editor,

Invasive fungal infections (IFI) are an increasingly frequent complication in patients admitted to intensive care units (ICU), and pose a serious challenge to the clinicians who attend critically ill patients.[1,2] The patientś outcome is directly influenced by the inter- and intra-individual pharmacokinetic variability, the need to optimize the antifungal delivery treatment according to site of infection, by emerging fluconazole and echinocandin-resistant *Candida* spp. infections, and by increasing azole-resistant *Aspergillus* spp. infections.[3,4] Liposomal amphotericin B (L-AmB) presents a good antifungal activity against *Candida* spp. and *Aspergillus* spp., and shows an important dose-dependent capability to accumulate in infected tissues, such as the liver, spleen, lung, kidneys and brain, at levels above the minimum inhibitory concentration.[5] L-AmB also shows a significant lesser risk of nephrotoxicity and fewer severe drug-related adverse events than conventional deoxycholate AmB.[6] Moreover, drug-drug interactions with L-AmB are irrelevant, which is an important factor in critically ill patients. Nonetheless, data on the use of L-AmB in the ICU is still lacking.

We have performed an observational and retrospective study which included all adult patients admitted to an ICU of a Spanish third-level hospital, and who received treatment with L-AmB for an IFI. The study inclusion period spanned from January 2022 to June 2023. Collected data included the patientsdemographics, characteristics of the IFI, antifungal treatment regimens prescribed, L-AMP-induced side effects and outcome. *Clinical improvement* was defined as amelioration of symptoms and signs associated to the IFI during treatment. *Microbiological success* was defined as the eradication of the fungal pathogen on the microbiological samples during treatment. *Mortality* was defined as any demise during follow-up, whereas *IFI-related mortality* was defined as any death related to IFI. *Adverse events* were defined as any occurrence of an undesirable event during or following the exposure to the L-AmB. *Acute renal injury* was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.[7] Quantitative variables are shown as mean (or median) ± standard deviation (or interquartile range), whereas qualitative variables are depicted as absolute and relative frequencies. The statistical analysis was carried out using SPSS v. 23.0 (BM Corp, Armonk, NY).

We have included 10 patients. Baseline and clinical characteristics are shown in Table 1. The mean age of the included patients was 53.6 ± 13.8 years. Five patients were considered to be immunosuppressed, including four liver transplant recipients. Three patients were treated for an invasive pulmonary aspergillosis (IPA), whereas seven received L-AmB for an invasive candidiasis (Table 2). The median time elapsed between the admittance in the ICU and the diagnosis of the IFI was 6.5 days (IQR 2–21.8). In two cases, the diagnosis was reached before the patient was admitted to the ICU. Two patients received a combined treatment of isavuconazole and L-AMP, whereas 7 were treated with a monotherapy regimen consisting of L-AmB. L-AmB was only used as first-line therapy in one patient, who had been diagnosed with a *Candida dubliniensis* meningitis infection. The main cause for the prescription of L-AmB was failure to improve with the first-line treatment (50.0%), mostly with anidulafungin. The median time elapsed between the start of the first-line antifungal treatment and the prescription of L-AmB was 16 days (IQR 4–30). The median duration of L-AmB treatment was 12 days (IQR 9–24), with a median dosage of 4.5 mg/kg/day (IQR 3.6–4.9). Two patients presented a L-AmB related side effect: one patient presented a case of hypokaliemia, which was managed with intravenous potassium supplementation, whereas another patient required a considerable number of blood transfusions due to anemia. It was not necessary to withdraw L-AmB due to side effects in any of the 10 patients. No cases of L-AmB-induced nephrotoxicity were diagnosed (serum creatinine levels, glomerular filtration rate, and nephrotoxic drugs co-administered with L-AmB are shown in Table S1 in Supplementary material). Clinical improvement was attained in 80% of patients. Only 1 patient did not achieve microbiological success. Although six patients (60%) eventually died during follow-up, IFI-related demise was only observed in one patient (10%). The median duration of admittance in the ICU was 35 days (IQR 12–70).

Our findings are similar to a retrospective study, which included 179 patients admitted to medical-surgical ICUs and treated with L-AmB for an IFI. The authors reported a 2% rate of severe adverse events and an in-hospital mortality rate of 59% (unfortunately, IFI-related death was not specified).[8] The 2016 Update by the Infectious Diseases Society of America Practice Guidelines for the Diagnosis and Management of Aspergillosis recommends L-AmB as an alternative primary therapy in patients in whom azole-resistant moulds, such as mucormycosis, is a concern, and as salvage treatment in patients who fail initial antifungal therapy.[9] In our case, L-

Table 1 Baseline characteristics of the ten patients included.

Patient number	1	2	3	4	5	6	7	8	9	10
Age (years)	25	55	56	54	81	56	60	45	50	54
Gender (M, F)	M	M	M	M	M	F	F	M	M	M
Underlying disease	LT	LT	HIV infection. Diffuse large-B cell lymphoma	LT	Urothelial carcinoma	Bariatric surgery. Anastomotic leak.	LT	Cardiac surgery postoperative care	No	Rectal adenocarcinoma
Diagnostic at ICU admission	Colonic perforation after EMR	Paracetamol-induced fulminant hepatic failure	Respiratory failure	Subarachnoid hemorrhage	Toxic-metabolic encephalopathy	Septic shock due to tertiary peritonitis	Liver retransplantation	Mitral and tricuspid valve annuloplasty and coronary revascularization	Mediastinitis due to a Boerhaave 's syndrome	Enterocutaneous fistula-related septic shock
SOFA score at ICU admission	5	16	4	8	8	2	6	–[a]	2	2
Immunosuppressive drugs previous IFI	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Type of immunosuppressive drugs previous IFI	Steroids, tacrolimus	Steroids, tacrolimus, basiliximab	R-CHOP + intrathecal chemotherapy (febrile neutropenia grade IV)	Steroids, tacrolimus, basiliximab	–	–	Steroids, basiliximab, tacrolimus	–	–	–
Use of KTR previous IFI	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No
Use of antibiotics previous IFI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Red blood cell transfusion previous IFI	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Length in ICU until IFI diagnosis (days)	2	10	Diagnosis performed previous ICU admittance	Diagnosis performed 48 h previous ICU admittance	3	12	64	25	1	2
Total length in ICU (days)	59	37	10	10	12	33	109	57	102	25

EMR: Endoscopic mucosal resection; HIV: human immunodeficiency virus; ICU: Intensive care unit; IFI: Invasive fungal infection; KRT: kidney replacement therapy; LT: liver transplantation; R-CHOP: cyclophosphamide, doxorubicin, hydrochloride and vincristine + rituximab.

[a] Admission was not sepsis-related.

Table 2 Characteristics of the fungal infection and the use of amphotericin B.

Patient number	1	2	3	4	5	6	7	8	9	10
Type IFI	IPA	IPA	IPA	Fungal meningitis	UTI	IC	IC	IC	IC	Secondary peritonitis
Type of yeast or mold isolated	*Aspergillus fumigatus*	*Aspergillus niger*	*Aspergillus* spp.	*Candida dubliniensis*	*C. albicans*	*C. glabrata*	*C. krusei* and *C. glabrata*	*C. albicans*	*C. glabrata* and *C. albicans*	*C. glabrata* and *C. tropicalis*
Diagnostic test	BAS	BAL	Positive GM in BAL	CSF	Urine culture	Blood culture	Blood culture	Mediastinum and pericardium biopsy	Pleural effusion	Peritoneal effusion
Antifungal regimen prescribed as first-line therapy	Isavuconazole	Isavuconazole	Anidulafungin	Amphotericin B and flucytosine	Fluconazole	Fluconazole, followed by anidulafungin	Anidulafungin	Anidulafungin	Anidulafungin	Fluconazole, followed by anidulafungin
Type of antifungal treatment	Combination treatment[a]	Combination treatment[a]	Monotherapy	Combination treatment	Monotherapy	Monotherapy	Monotherapy	Monotherapy	Monotherapy	Monotherapy
Time span until amphotericin B switch/added to treatment (days)	3	13	16	–	1	26	33	28	33	5
Indication for switching/adding amphotericin B treatment	Suspected mucormycosis infection	Failure of improvement during azole treatment	Development of a new thoracic infiltrate and persistence of fever	–	Use of KRT	Chorioretinitis	Treatment failure after one month of anidulafungin	Treatment failure after one month of anidulafungin	Echinocandin-resistant yeast and anidulafungin-induced hepatic toxicity	Improve antifungal penetration in peritoneum
Median dose of amphotericin B administered (mg/kg/day)	4	5	3.8	4.5	1.5	4.8	4.5	3	4.5	5
Duration of therapy with amphotericin B (days)	11	13	13	11	7	22	30	4	52	10
Amphotericin B-induced side effects	No	No	No	No	No	Hypokalemia	No	No	Anemia[b]	No
Clinical improvement	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Microbiological success	Yes	Unknown[c]	Yes	No	Yes	Yes	Yes	Unknown[c]	Yes	Yes
Patient́s outcome at the end of follow-up	Alive	Decease	Decease	Decease	Decease	Alive	Decease	Decease	Alive	Alive
Cause of death[d]	–	MOF	Respiratory failure due to end-stage oncological disease	Ischemic encephalopathy	Mesenteric ischemia	–	Septic shock	Hemorrhagic shock	–	–

AT: Aspergillus tracheobronchitis; BAL: broncoalveolar lavage; BAS: bronchial aspirate; CSF: Cerebrospinal fluid; GM: galactomannan; IC: invasive candidiasis; IFI: invasive fungal infection; IPA: invasive pulmonary aspergilosis; KRT: kidney replacement therapy; MOF: multiorganic failure.

[a] Amphotericin B was added to isavuconazole as treatment of IFI.

[b] Considerable increase in blood transfusion demands after amphotericin B was initiated.

[c] No microbiological samples were collected after amphotericin B was prescribed.

[d] Death was only related to the IFI in patient 2.

AmB was prescribed in one suspected case of mucormycosis, and in two cases of IPA refractory to azoles and echinocandins, respectively. Interestingly, L-AmB was prescribed in one patient after failure of clinical and microbiological improvement of an intra-abdominal candidiasis (IAC) while on anidulafungin treatment, whereas in another patient the echinocandin was switched to L-AmB in order to optimize the treatment of *Candida* peritonitis. Recent studies, have highlighted that echinocandins show poor diffusion in the peritoneal fluid of post-surgical critically ill patients,[10] and that the abdominal cavity could play a pivotal niche in the emergence of *Candida*-resistance strains.11 As such, some authors now recommend L-AmB as an alternative treatment to echinocandins in the case of IAC, especially in critically ill patients.[12] The two patients diagnosed with an IAC were considered to be microbiological and clinical cured after L-AMB treatment, without L-AMB related adverse events. Our study has limitations that must be taken into account. The most important limitation derives from the rather small number of included patients. Nonetheless, the median days of the L-AmB treatment and of the follow-up period can be considered large enough to allow for a thorough evaluation of the safety profile of L-AmB.

In conclusion, L-AmB, used as first-line or as rescue treatment, proved to be a very effective antifungal drug in critically ill patients, with a good tolerability profile and manageable adverse events. L-AmB resulted to be a particular reliable treatment option in ICU patients with difficult-to-treat IFI, such as IAC.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medin.2024.08.006.

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https://doi.org/10.1016/j.medin.2024.08.006