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Safety of different amphotericin B formulations among AIDS patients with invasive fungal disease: a retrospective observational study

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Abstract

We conducted a retrospective, observational study among acquired immune deficiency syndrome (AIDS) patients with cryptococcal meningitis or talaromycosis to assess AmB formulations-related adverse events (AEs). Total 205 eligible patients were enrolled. Of them, 139 received AmB therapy, 51 received liposomal AmB (L-AmB) therapy, and 15 received AmB cholesteryl sulfate complex (ABCD) therapy. The incidences of total AEs between the AmB, L-AmB and ABCD group had no significant differences. The ABCD group had significantly higher incidences of hepatotoxicity and hematological toxicity than the AmB and L-AmB groups. The incidence of grade 3–4 hematological toxicity in the ABCD group was significantly higher than that in the AmB and L-AmB groups. Multinomial logistic regression models showed that compared with AmB, ABCD had a higher risk for the occurrence of grade 3–4 hematological toxicity (aOR = 43.924, 95%CI 6.296-306.418; $p < 0.001$). We demonstrated that ABCD was more prone to hepatotoxicity and hematological toxicity than AmB and L-AmB among AIDS patients, which is worth noting.

Keywords Amphotericin B, Liposomal AmB, AmB cholesteryl sulfate complex, Safety, Hematological toxicity

Introduction

Acquired immune deficiency syndrome (AIDS) patients are one of the most susceptible groups to invasive fungal disease (IFD), with high mortality and morbidity. It is reported that about 50% of opportunistic infections among HIV-positive people are caused by fungi [1]. Cryptococcal meningitis and talaromycosis are common IFD in AIDS patients. Amphotericin B (AmB) is preferred for cryptococcal meningitis and talaromycosis by guidelines [2]. However, drug-induced toxicity may limit its clinical application. Liposomal AmB (L-AmB) has been reported to have lower incidences of adverse events (AEs) than AmB due to its chemical composition and rigorous manufacturing standards [3, 4]. In addition, AmB cholesteryl sulfate complex (ABCD) has also been used in

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treating IFD in China, which was described to have good efficacy and safety in the treatment of IFD in 30 patients with hematological malignancies [5]. Here we conducted a retrospective observational study to compare the drug-related AEs between AmB, L-AmB and ABCD therapy in AIDS patients with cryptococcal meningitis or talaromycosis, and the potential risks associated with the drug-related hematological toxicity were analyzed.

Methods

Between January 1, 2018, and April 30, 2023, AIDS patients who had confirmed diagnosis with cryptococcal meningitis or talaromycosis were retrospectively recruited from Zhongnan Hospital of Wuhan University, Hubei and Hunan university of medicine general hospital, Hunan. Patients whose age≥18 years old and who received treatment with AmB or L-AmB or ABCD were included. The exclusion criteria were as follows: (1) discharged or died on the day of AmB/L-AmB/ABCD initiation; (2) AmB, L-AmB and ABCD were exchanged during the treatment. The regimens of AmB, L-AmB and ABCD in all patients were based on our guideline [2]. For patients with cryptococcal meningitis, AmB (0.5 ~ 0.7 mg/kg/d, North China pharmaceutical co.,ltd, China) or L-AmB (3 ~ 5 mg/kg/d, Ben Venue Laboratories Inc, USA) or ABCD (4 ~ 6 mg/kg/d, Unacon ouyi drug co., ltd, China) were injected in the induction period for at least 4 weeks, combining with flucytosine. For patients with talaromycosis, AmB or L-AmB or ABCD were injected in the induction period for 2 weeks.

AmB/L-AmB/ABCD related AEs were evaluated within 7 days after drug withdrawal. Drug-related AEs were divided to 4 grades [6, 7]: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life-threatening; Grade 5, fatal. Hematological toxicity were graded according to the internationalwork shop on chronic lymphocytic leukemia (IWCLL) Working Group grading scale [7], and the other AEs including hepatotoxicity and nephrotoxicity were graded according to DAIDS Adverse Event Grading Tables (Version 2.1) [6]. In cases of pre-existent laboratory examination abnormalities, an increase in DAIDS or IWCLL grade was considered an drug-related AE. The judgement of AmB/L-AmB/ABCD related AEs was independently decided by two clinical experts, and when it was inconsistent, senior experts would issue a unified opinion.

SPSS 21.0 was used for data statistics. Variables were denoted as medians (IQR) or n (%). Group t-test or non-parametric rank sum test was used for the analyses of continuous variables according to Kolmogorov-Smirnov test, and chi-square test or Kruskal-Wallis rank sum test was used for the analyses of counts data. The potential risks associated with the drug-related AEs (no AEs; grade 1–2 AEs; grade 3–4 AEs) were performed by multinomial logistic regression model after the hypothesis of equal coefficients of independent variables tested by parallel lines. $p<0.05$ was considered statistically significant.

Results

205 eligible patients who met the inclusion and exclusion criteria were enrolled in the study. 139 received AmB, 51 received L-AmB and 15 received ABCD therapy. Majority of patients (≥80%) in both three groups were males, and most patients (≥80%) didn't initiate ART. The median duration on ART in the AmB, L-AmB and ABCD groups were 1.2, 2.0 and 3.5 months, respectively. The characteristics among these patients were shown in Additional file 1.

The comparisons of AmB, L-AmB and ABCD-related AEs were shown in Table 1. The incidence of infusion-related reactions was significantly lower in the L-AmB group than in the AmB ($p=0.04$) and ABCD groups

Table 1 Comparison of total AEs between the three groups

	AmB	L-AmB	ABCD	*p* value		
	(*n* = 139)	(*n* = 51)	(*n* = 15)	AmB vs. L-AmB	AmB vs. ABCD	L-AmB vs. ABCD
Total AEs, n(%)	125 (89.9)	44 (86.3)	15 (100.0)	0.48	0.36	0.34
Infusion-related reactions, n(%)	32 (23.0)	5 (9.8)	5 (33.3)	**0.04**	0.37	**0.02**
Rash, n(%)	11 (7.9)	0 (0.0)	0 (0.0)	**0.04**	0.60	/
Anaphylactic shock, n(%)	1 (0.7)	0 (0.0)	0 (0.0)	1.00	1.00	/
Electrolyte disturbance, n(%)	49 (35.2)	24 (47.0)	12 (80.0)	0.14	**0.002**	**0.05**
Hypokalemia, n(%)	49 (35.2)	24 (47.0)	12 (80.0)	0.14	**0.002**	**0.05**
Cardiac toxicity, n(%)	2 (1.4)	0 (0.0)	0 (0.0)	1.00	1.00	/
Tachycardia, n(%)	2 (1.4)	0 (0.0)	0 (0.0)	1.00	1.00	/
Hepatotoxicity, n(%)	33 (23.7)	7 (13.7)	8 (53.3)	0.13	**0.01**	**0.001**
Nephrotoxicity, n(%)	86 (61.9)	23 (45.1)	7 (46.7)	**0.04**	0.28	1.00
Hematological toxicity, n(%)	37 (26.6)	13 (25.5)	11 (73.3)	0.87	**0.001**	**0.002**
Neutropenia, n(%)	13 (9.3)	2 (3.9)	9 (60.0)	0.35	**< 0.001**	**< 0.001**
Hypohemoglobin, n(%)	33 (23.7)	11 (21.5)	8 (53.3)	0.75	**0.01**	**0.02**
Thrombocytopenia, n(%)	11 (7.9)	2 (3.9)	8 (53.3)	0.52	**< 0.001**	**< 0.001**

Table 2 Comparisons of grade 3–4 AEs between the three groups

	AmB	L-AmB	ABCD	*p* value		
	(*n* = 139)	(*n* = 51)	(*n* = 15)	AmB vs. L-AmB	AmB vs. ABCD	L-AmB vs. ABCD
Total grade 3–4 AEs, n(%)	50 (36.0)	9 (17.6)	10 (66.7)	**0.02**	**0.02**	**0.001**
Grade 3, n(%)	32 (23.0)	7 (13.7)	2 (13.3)	0.16	0.59	1.00
Grade 4, n(%)	18 (12.9)	2 (3.9)	8 (53.3)	0.13	**< 0.001**	**< 0.001**
Grade 3–4 hepatotoxicity, n(%)	2 (1.4)	0 (0.0)	0 (0.0)	1.00	1.00	/
Grade 3, n(%)	2 (1.4)	0 (0.0)	0 (0.0)	1.00	1.00	/
Grade 4, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	/	**/**	/
Grade 3–4 nephrotoxicity, n(%)	37 (26.6)	6 (11.8)	4 (26.7)	**0.03**	1.00	0.31
Grade 3, n(%)	23 (16.5)	4 (7.8)	2 (13.3)	0.20	1.00	0.89
Grade 4, n(%)	14 (10.1)	2 (3.9)	2 (13.3)	0.29	1.00	0.47
Grade 3–4 hematological toxicity, n(%)	13 (9.3)	1 (2.0)	10 (66.7)	0.16	**< 0.001**	**< 0.001**
Grade 3, n(%)	9 (6.5)	1 (2.0)	2 (13.3)	0.38	0.65	0.25
Grade 4, n(%)	4 (2.9)	0 (0.0)	8 (53.3)	0.57	**0.001**	**< 0.001**
Grade 3–4 neutropenia, n(%)	6 (4.3)	0 (0.0)	8 (53.3)	0.19	**0.008**	**< 0.001**
Grade 3, n(%)	3 (2.1)	0 (0.0)	3 (20)	0.56	**0.007**	**0.01**
Grade 4, n(%)	3 (2.1)	0 (0.0)	5 (33.3)	0.56	**< 0.001**	**< 0.001**
Grade 3–4 hypohemoglobin, n(%)	4 (2.9)	0 (0.0)	0 (0.0)	0.57	1.00	**/**
Grade 3, n(%)	4 (2.9)	0 (0.0)	0 (0.0)	0.57	1.00	**/**
Grade 4, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	/	**/**	**/**
Grade 3–4 thrombocytopenia, n(%)	5 (3.6)	1 (2.0)	6 (40.0)	0.92	**< 0.001**	**< 0.001**
Grade 3, n(%)	4 (2.9)	1 (2.0)	2 (13.3)	1.00	0.20	0.25
Grade 4, n(%)	1 (0.7)	0 (0.0)	4 (26.7)	1.00	**< 0.001**	**0.002**

(p=0.02). The ABCD group had significantly higher incidences of hypokalemia (p=0.002; p=0.05), hepatotoxicity (p=0.01; p=0.001) and hematological toxicity (p=0.001; p=0.002) than the AmB and L-AmB groups.

The incidences of total grade 3–4 AEs (p=0.02; p=0.001) and grade 4 AEs (p<0.001; p<0.001) in the ABCD group were significantly higher than that in the AmB and L-AmB groups. The incidences of grade 3–4 hepatotoxicity had no significant differences between the three groups. The incidences of grade 3–4 hematological toxicity (p<0.001; p<0.001) and grade 4 hematological toxicity (p=0.001; p<0.001), mainly neutropenia and thrombocytopenia, in the ABCD group were significantly higher than that in the AmB and L-AmB groups. No grade 5 AEs were observed in all three groups. Multinomial logistic regression models showed that compared with AmB, ABCD had a higher risk for the occurrence of grade 3–4 hematological toxicity (aOR=43.924, 95%CI 6.296-306.418; p<0.001), see in Additional file 2).

Discussion

The AmB lipid-associated formulations, including L-AmB and ABCD, has been developed to solve the issue on the increased toxicity related to AmB. However, the safety of these drugs in AIDS patients haven't been fully studied. This retrospective, observational study aimed at comparing the safety of AmB, L-AmB, and ABCD among AIDS patients with cryptococcal meningitis and talaromycosis in order to provide reference for clinical practice.

Our study found that the incidences of infusion-related reactions in the ABCD group were higher than that in the AmB and L-AmB group, which was consistent with the results of other studies [8, 9]. Up-regulation of IL-1β protein synthesis and decreasing IL-1ra levels may be responsible for the increased infusion-related toxic adverse effects among patients with ABCD therapy [10].

ABCD could be quickly absorbed by organs of reticuloendothelial system (such as liver, spleen and lung) after entering the blood, thus avoiding damage to renal tubules; therefore, nephrotoxicity was low by comparison with AmB [8, 11]. Studies conducted in patients with aspergillosis showed that ABCD may have superior renal safety compared with AmB [9, 12]. Our study observed that the incidence of ABCD-related nephrotoxicity was lower than AmB, however, there were no significant differences of the incidence of nephrotoxicity in the ABCD group by comparison with the AmB and L-AmB groups. Larger sample size studies are needed to investigate the renal safety of ABCD.

We also observed higher rates of hepatotoxicity, mainly grade 1–2 hepatotoxicity in the ABCD group compared with the AmB and L-AmB groups. A randomized, double-blind, multicenter trial comparing L-AmB with AmB for empirical antifungal therapy found no significant difference in the frequency of hepatotoxicity between L-AmB and AmB [13]. A meta-analysis on AmB formulations therapy for invasive fungal infection showed that patients receiving empirical therapy with ABCD, AmB

lipid complex (ABLC), and L-AmB had higher pooled risk for developing mildly elevated liver enzymes in comparison to AmB [14]. Combined with our results, ABCD-induced hepatotoxicity should be concerned in the treatment of IFD among AIDS patients.

It's noteworthy that the ABCD-related hematological toxicity, especially the grade 3–4 hematological toxicity including neutropenia and thrombocytopenia, in our study were significantly higher than AmB and L-AmB. Our multinomial logistic regression analysis also supported the data. The incidence of AmB related anemia was as high as 75%, which may be partly due to the suppression of erythropoietin production [15, 16]. Previous studies found that the incidences of neutropenia, hypohemoglobin and thrombocytopenia were lower in patients with L-AmB treatment compared with patients with AmB treatment, and ABLC had more obvious neutropenia and thrombocytopenia side effects [17, 18]. Although ABCD has been evaluated in limited studies and found to be safe in immunocompromised patients with IFD [9, 11, 19, 20], there is no data on ABCD-related hematological toxicity. Our data demonstrated that ABCD-related hematological toxicity including neutropenia, hypohemoglobin and thrombocytopenia should be of great attention. The mechanism of ABCD-induced hematological toxicity remains obscure, which needs more large sample sizes studies to further investigate.

In conclusion, L-AmB should be preferred for treatment in AIDS patients with IFD for its fewer AEs compared with AmB and ABCD. ABCD-related hematological toxicity, including neutropenia, hypohemoglobin and thrombocytopenia, should be particularly noteworthy.

Abbreviations

AIDS	acquired immune deficiency syndrome
IFD	invasive fungal disease
AmB	amphotericin B
L-AmB	liposomal AmB
AEs	adverse events
ABCD	AmB cholesteryl sulfate complex
IWCLL	international work shop on chronic lymphocytic leukemia
mNGS	metagenomic next-generation sequencing
IQR	interquartile range
ABLC	AmB lipid complex

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

KL and HY conceptualized the study. YT, YM, SW, MT, SS and JL contributed to data collection. SW performed data analysis. YT, YM, KL and HY wrote the manuscript. YT, HY, SW, HY and KL have accessed and verified the underlying data. HY and KL had full access to all the data in the study. The corresponding authors had final responsibility for the decision to submit for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of Zhongnan Hospital of Wuhan University (2024036 K).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Rajasingham R, Govender NP, Jordan A, Loyse A, Shroufi A, Denning DW et al. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis[J]. Lancet Infect Dis 2022,22(12):1748–55. https://doi.org/10.1016/S1473-3099(22)00499-6
2. AIDS and, Hepatitis C, Group ID, Branch CM, Association. China Center for Disease Control and Prevention. Guidelines for AIDS diagnosis and treatment in China (2021 Edition) [J]. Chin J Intern Med. 2021;60(12):1106–28. https://doi.org/10.3760/CMA.J.CN112138-28.
3. Groll AH, Rijnders BJA, Walsh TJ, Adler-Moore J, Lewis RE, Brüggemann RJM. Clinical pharmacokinetics, Pharmacodynamics, Safety and Efficacy of Liposomal Amphotericin B[J]. Clin Infect Dis 2019,68(Suppl 4):S260–74. https://doi.org/10.1093/cid/ciz076
4. Adler-Moore J, Lewis RE, Brüggemann RJM, Rijnders BJA, Groll AH, Walsh TJ. Preclinical safety, tolerability, Pharmacokinetics, Pharmacodynamics, and antifungal activity of liposomal amphotericin B[J]. Clin Infect Dis 2019,68(Suppl 4):S244–59. https://doi.org/10.1093/cid/ciz064
5. Wang J, Jin S, Wu XJ, Miao M, Tang XW, He XF et al. Clinical analysis of amphotericin B CSC for injection in the treatment of invasive fungal disease for patients with hematological malignancies in 30 cases[J]. Zhonghua Xue Ye Xue Za Zhi 2022,43(10):848–52. https://doi.org/10.3760/cma.j.issn.0253-2727.2022.10.008
6. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf
7. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446–56. https://doi.org/10.1182/blood-2007-06-093906.

8. Hamill RJ, Amphotericin B. Formulations: a comparative review of efficacy and toxicity[J]. Drugs 2013,73(9):919–34. https://doi.org/10.1007/s40265-013-0069-4
9. Paterson DL, David K, Mrsic M, Cetkovsky P, Weng XH, Sterba J et al. Premedication practices and incidence of infusion-related reactions in patients receiving AMPHOTEC: data from the Patient Registry of Amphotericin B Cholesteryl Sulfate Complex for Injection Clinical Tolerability (PRoACT) registry[J]. J Antimicrob Chemother 2008,62(6):1392–400. https://doi.org/10.1093/jac/dkn394
10. Simitsopoulou M, Roilides E, Dotis J, Dalakiouridou M, Dudkova F, Andreadou E et al. Differential expression of cytokines and chemokines in human monocytes induced by lipid formulations of amphotericin B[J]. Antimicrob Agents Chemother 2005,49(4):1397–403. https://doi.org/10.1128/AAC.49.4.1397-1403.2005
11. Oppenheim BA, Herbrecht R, Kusne S. The safety and efficacy of amphotericin B colloidal dispersion in the treatment of invasive mycoses[J]. Clin Infect Dis 1995,21(5):1145–53. https://doi.org/10.1093/clinids/21.5.1145
12. White MH, Anaissie EJ, Kusne S, Wingard JR, Hiemenz JW, Cantor A et al. Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis[J]. Clin Infect Dis 1997,24(4):635–42.
13. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious diseases mycoses Study Group[J]. N Engl J Med. 1999;340(10):764–71. https://doi.org/10.1056/NEJM199903113401004.
14. Wang JL, Chang CH, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection[J]. Antimicrob Agents Chemother 2010,54(6):2409–19. https://doi.org/10.1128/AAC.01657-09
15. Tugume L, Morawski BM, Abassi M, Bahr NC, Kiggundu R, Nabeta HW, et al. Prognostic implications of baseline anaemia and changes in haemoglobin concentrations with amphotericin B therapy for cryptococcal meningitis[J]. HIV Med. 2017;18(1):13–20. https://doi.org/10.1111/hiv.12387.
16. Lin AC, Goldwasser E, Bernard EM, Chapman SW. Amphotericin B blunts erythropoietin response to anemia[J]. J Infect Dis 1990,161(2):348–51. https://doi.org/10.1093/infdis/161.2.348
17. Shigemi A, Matsumoto K, Ikawa K, Yaji K, Shimodozono Y, Morikawa N et al. Safety analysis of liposomal amphotericin B in adult patients: anaemia, thrombocytopenia, nephrotoxicity, hepatotoxicity and hypokalaemia[J]. Int J Antimicrob Agents 2011,38(5):417–20. https://doi.org/10.1016/j.ijantimicag.2011.07.004
18. Falci DR, Da RF, Pasqualotto AC. Hematological toxicities associated with amphotericin B formulations[J]. Leuk Lymphoma 2015,56(10):2889–94. https://doi.org/10.3109/10428194.2015.1010080
19. Liu J, Ma X. Amphotericin B colloidal dispersion: an effective drug for the treatment of mucormycosis in China[J]. Front Cell Infect Microbiol 2023,13:1147624. https://doi.org/10.3389/fcimb.2023.1147624
20. Guo LS. Amphotericin B colloidal dispersion: an improved antifungal therapy[J]. Adv Drug Deliv Rev. 2001;47(2–3):149–63. https://doi.org/10.1016/s0169-409x(01)00104-1.

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