Real-world dataset demonstrates favorable safety profile of liposomal amphotericin B for the treatment of invasive aspergillosis in high-risk haemato-oncology patients

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Background

Liposomal amphotericin B (Ambisome®) (LAmB) remains a cornerstone treatment for invasive fungal disease, due to its broad spectrum of activity, proven efficacy and lack of resistance. Evidence shows a significantly reduced risk of adverse events (AEs) over conventional AmB and other lipid formulations. LAmB is an alternative to voriconazole (VOR) for first-line treatment of invasive aspergillosis (IA), in cases of hepatotoxicity, dermatologic or visual AEs or QTc prolongation. This largest available real world evidence (RWE) study evaluates the AE profiles of LAmB and VOR in the high-risk haemato-oncology setting.

Methods

This retrospective observational drug utilization study collected data from patient's medical records. Adult haemato-oncology patients (pts) were included who received ≥1 dose of LAmB or VOR for first-line treatment of proven/probable IA (January 2014 - December 2019), in accordance to local clinical practice. Follow-up period was 84 (±7) days or until lost-to-follow up or death. The following were collected: nephrotoxicity (leading to new renal replacement therapy, persistent renal dysfunction or death), hepatotoxicity (leading to hepatic failure, jaundice cholestatic, cholecystitis or death), AEs leading to treatment modification or discontinuation (D/C), concomitant nephrotoxic or hepatotoxic medication, baseline comorbidities (diabetes mellitus [DM], renal disease/injury, liver disease/injury or underlying immunosuppression).

Results

359 pts were included: 127 received LAmB, 232 VOR. Table 1 shows patient and treatment characteristics, haemato-oncological conditions, comorbidities and concomitant medication at baseline. Two pts (1.6%) in the LAmb group had mild nephrotoxicity, one was considered treatment-related by the investigator, resulting in dose modification. Six pts (2.6%) in the VOR group had nephrotoxicity, none treatment-related. One LAmB pt (0.8%) and 13 VOR pts (5.6%) had hepatotoxicity; in the VOR group 10 were treatment-related (3 severe/life threatening; 5 resulted in D/C). Of all pts treated with LAmB, 4.7% (6 pts) D/C due to any other AE considered linked to study treatment. For VOR, this was 10.7% (25 pts).

Conclusions

This large real-world dataset demonstrates that the occurrence of treatment-related nephrotoxic and hepatotoxic events is rare in high-risk haemato-oncology patients treated with LAmB for IA.

Table 1: Descriptive overview of haemato-oncology patients treated with LAmB or VOR for IA, included from 15 hospitals across Belgium, France, Germany, Spain & UK

Characteristics	LAmB (n=127)	VOR (n=232)
Baseline Patient & disease characteristics		
Age at diagnosis (years) – Mean (range)	54 (20-81)	58 (19-87)
Gender – Male – N (%)	81 (63.8)	132 (56.9)
Weight (kg) – Mean (range)	72.0 (38.7 - 123)	70.8 (38.0-160.0)
IA - proven/probable/unknown (%)	30.7 / 69.3 / 0.0	14.2 / 84.9 / 0.9
Neutropenia (<500 neutrophils/µL) – N (%)	54 (42.5)	105 (45.3)
Comorbidities at baseline – N (%)		
Diabetes mellitus	13 (10.2)	29 (12.5)
Renal disease/injury	16 (12.6)	31 (13.4)
Liver disease/injury	21 (16.5)	31 (13.4)
Other immunosuppressive comorbidities	48 (37.8)	58 (25.0)
Underlying haemato-oncological condition – N (%)		
AML	66 (52.0)	149 (64.2)
ALL	23 (18.1)	25 (10.8)
MDS	26 (20.5)	38 (16.4)
Allo-HSCT	59 (46.5)	83 (35.8)
Other haematological disorder needing HSCT	17 (13.4)	34 (14.7)
Treatment characteristics		
Study treatment		
Route of administration – IV – N (%)	127 (100)	163 (70.3)
Dose (mg) – Average (range)	246 (50-750)	299 (83.7-1000)
Dose (mg/kg) – Average (range)	3.5 (0.8-10)	4.2 (1.2-10.4)
Days of first-line treatment – Average (range)	18.7 (1-91)	25.9 (1-92)
Concomitant medication at baseline – N (%)		
Patients with ≥ 1 nephrotoxic concomitant medication	36 (28.3)	56 (24.1)
Patients with ≥ 1 hepatotoxic concomitant medication	23 (18.1)	34 (14.7)
Patients with ≥ 1 nephrotoxic & hepatotoxic concomitant medication	1 (<1)	15 (6.5)
Adverse events		
Pts with nephrotoxicity during study treatment - N (%)	2 (1.6)	6 (2.6)
Pts with treatment-related renal toxicity – N (%)	1 (50)	0 (0)
Concomitant nephrotoxic medication – N (%)	0 (0)	N/A
Duration of study treatment before AE (days) – N	15	N/A
Severity (Life threatening / Severe / Moderate / Mild) – N (%)	0 / 0 / 0 / 1 (100)	N/A
AE resulting in dose modification – N (%)	1 (100)	N/A
AE resulting in treatment D/C – N (%)	0	N/A
Pts with hepatotoxicity during study treatment – N (%)	1 (0.8)	13 (5.6)
Pts with treatment-related hepatotoxicity – N (%)	0 (0)	10 (76.9)
Concomitant hepatotoxic medication – N (%)	N/A	3 (30)
Duration of study treatment before AE (days) – Average (range		24.2 (3 - 69)
Severity (Life-threatening / Severe / Moderate / Mild) – N (%)	N/A	1 (10) / 2 (20) / 6 (60) / 1 (10)
AE resulting in dose modification – N (%)	N/A	0
AE resulting in treatment D/C – N (%)	N/A	5 (50)
Study treatment D/C due to AE – N (%)	6 (4.7)	25 (10.7)

Abbreviations:
ALL = acute lymphoblastic leukaemia; allo-HSCT = allogeneic haematopoietic stem cell transplantation; AML = acute myeloid leukaemia; D/C = discontinuation; IA = invasive aspergillosis; IV = intravenous; LAmB = Liposomal Amphotericin B (Ambisome®); MDS = myelodysplastic syndrome; N/A = not applicable; VOR = voriconazole

Definitions:
- *nephrotoxicity: leading to new renal replacement therapy, persistent renal dysfunction or death*
- *hepatotoxicity: leading to hepatic failure, jaundice cholestatic, cholecystitis or death*

References

Cornely et al. CID 2007; Falci et al. Mycoses 2015; Ullmann et al. Curr Med Res Opin 2003