High loading dose AmBisome® is efficacious and well tolerated in the management of invasive fungal infection in hematology patients

Despite improved supportive care, and the introduction of less toxic lipid-formulations of amphotericin B deoxycholate and other new antifungal agents the mortality from invasive fungal infection (IFI) in hematology patients remains high. New management strategies are therefore required to improve outcome.

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Data from animal models suggest that, compared with standard dose, higher doses of liposomal amphotericin (LAmB) (10 mg/kg/day) reduce the fungal burden[1] and that up-front loading doses may improve survival.[2,3] In humans, 10 mg/kg/day achieves maximum plasma concentrations and is well tolerated.[4] In view of this promising animal model data and evidence of clinical tolerability, we performed an open label, non-comparative, multicentred study to evaluate the efficacy of high loading dose AmBisome® in the treatment of hematology patients with proven and probable IFI.

Approval for the study was obtained from the relevant ethics committees and full informed consent was obtained. Between February 2002 and December 2004, 43 patients, ≥2 years of age, receiving intensive chemotherapy, or stem cell transplantation (SCT) for hematologic malignancy, with proven or probable IFI were recruited. Patients received AmBisome® 10 mg/kg/day for 5 days followed by 3 mg/kg/day for 9 days (primary treatment period). Thereafter, treatment was at the discretion of the attending physician (secondary treatment period). Efficacy was assessed by clinical response and survival at day 15 (end of primary treatment period) and at the end of the secondary treatment period. Responses were defined as previously published:[5] complete response (CR), complete resolution of clinical signs and symptoms of IFI; partial response (PR), reduction in severity or number of pre-treatment signs and symptoms of IFI; or failure, lack of efficacy of the treatment, death attributable to IFI or failure to achieve CR/PR. Thirty-four out of 43 patients were evaluable (Table 1). Six failed to meet the definitions of proven or probable IFI; 2 case report forms were incomplete; and 1 was excluded due to chest tightness and a decrease in oxygen saturations (89%) during the administration of AmBisome®.

According to the proposed European Organisation for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) definitions of IFI, 2 patients had proven invasive mould infection (IMI) both presenting with sinus infections (*Rhizopus arrhizus* and *Aspergillus fumigatus*) and 32 had probable IFI (1 sinus and 31 pulmonary infections). Positive fungal microbiology, including aspergillus galactomannan (GM), was obtained in 13 out of 32 with probable IFI (7 *Aspergillus spp.* and 4 *Candida spp.*, cultured and 2 positive GM). Based on clinical, radiological and microbiological evidence, 30 out of 34 were thought to have IMI, and the other 4, invasive candidiasis.

Patients received a median of 27 days (mean 41, range 2-192) of therapy with AmBisome®. The overall response (CR and PR) at day 15 was 68% with an overall survival of 88% (61% and 90% respectively for allogeneic SCT recipients). Four patients (12%) died due to IFI before day 15. The overall response (CR and PR) and overall survival at the end of the secondary treatment period were 62% (61% for allogeneic SCT recipients) and 74% (61% for allogeneic SCT recipients) respectively. IFI was responsible for or contributed to the death in 8 of the 13 deceased patients. Relapsed disease was responsible for the other patient deaths.

Table 1. Study patient characteristics.

Patient characteristics	*n=34*
Sex	
Male	19
Female	15
Age	
Range	7-68 years
Median	39 years
≤18 years	11
> 18 years	23
Underlying condition	
Acute myeloid leukemia	13
Acute lymphoblastic leukemia	5
Chronic lymphocytic leukemia	3
Chronic myeloid leukemia	3
Lymphoma	4
Myelodysplastic syndrome	2
Others	4
(β thalassemia, aplastic anemia, dyskeratosis congenita, Waldenströms macroglobulinemia)	
Post allogeneic SCT	18
Relapsed disease	7

It is important to note that when this study was designed only proposed EORTC/MSG definitions for IFI were available. Subsequently, in 2002, modified definitions were published.[6] These no longer included the microbiological criterion *pulmonary abnormality and negative bacterial cultures of any possible bacteria from any specimen relating to the lower respiratory tract including blood, sputum and BAL*. This modification had an impact on the certainty with which IFI is defined[7] and if applied to our study population cases of IFI would be re-classified as follows: 2 proven, 13 probable and 19 possible. For the 15 cases of re-classified proven and probable IFI, the day 15 and the end treatment response rates were 53% and 47% respectively.

Toxicity is presented in Table 2. Nephrotoxicity was the most common side effect (32%) and related data was similar in the SCT (28%), overall (32%), adult (30%) and pediatric (36%) populations. The median increase in creatinine was 1.6 times baseline (mean 1.7, range 0-6.8) and was similar irrespective of the concomitant administration of other nephrotoxic drugs. No patient required dialysis; however, 1 patient was switched to caspofungin. Liver dysfunction was also relatively common (24%), and in 2 patients, AmBisome® was discontinued.

Response rates in our study of high loading dose AmBisome® compare favourably with other studies which do not utilise loading doses[8] suggesting this may be a valid approach. However, in a study published in abstract format which randomized patients to standard or high dose antifungal therapy (3 or 10 mg/kg/day of LAmB for 14 days) there was no significant difference in favourable overall response or 12 week survival. Furthermore, there was increased nephrotoxicity in the

Table 2. Toxicity.

Side effect	No. of patients (%)*
Nephrotoxicity (x2 baseline creatinine)†	11/34 (32)
Dialysis support	0 (0)
Abnormal liver function tests‡	8 (24)
Increased bilirubin	1
Increased alanine aminotransferase	1
Increased aspartate aminotransferase	2
Increased alkaline phosphatase	7 (21)¶
Fever	2 (6)
Skin rash	4 (12)
Hearing loss§	1 (3)
Myalgia	1 (3)
Hypokalemia	2 (6)
Chest tightness	1 (3)
Nausea	2 (6)

**The attending physician removed 1 patient from the study, due to an infusion-related adverse event with chest tightness and transient hypoxia.†Two of the 34 had AmBisome® for only 2 and 3 days respectively; nephrotoxicity may have occurred if treatment had continued for longer. Four of the 11 that developed nephrotoxicity were ≤18 years. Five of the 11 patients with nephrotoxicity were allogeneic SCT recipients; therefore nephrotoxicity was no more common in this subgroup. ‡Several patients had more than one abnormal parameter. §There was one clinical report of hearing loss, however, this parameter was not routinely measured. ¶Using World Health Organisation toxicity criteria: 2 grade 1; 4 grade 2; and 1 grade 3.*

high dose arm.[9] The extended duration of high dose LAmB (14 days compared with 5 days administered in our study) may have increased toxicity and limited further administration of LAmB.

In conclusion, the data presented in this study demonstrate that high loading dose AmBisome® is efficacious and well tolerated in the management of IFI although escalating cost may limit this approach.

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