Efficacy of liposomal amphotericin B alone or in combination with caspofungin versus caspofungin alone or caspofungin followed by liposomal amphotericin B for treatment of murine Candida parapsilosis infection


Objectives: Given the increased incidence of Candida glabrata and Candida parapsilosis infections, the limited efficacy of echinocandins against C. parapsilosis and the reported synergy of caspofungin (Cs) and liposomal amphotericin B (LAB) for treating murine C. glabrata infection, we tested this latter combination in a murine C. parapsilosis systemic infection to try to improve treatment outcome. Methods: A broth microdilution assay was used to determine the C. parapsilosis (ATCC 22019) MIC of LAB (AmBisome®) and Cs (Cancidas®). Swiss Webster mice were challenged i.v. with 3.5 X 10^7 C. parapsilosis, and daily treatment initiated 24h later with one of the following regimens: 5 or 7.5 mg/kg LAB, 1 mg/kg Cs, 5 or 7.5 mg/kg LAB + 1 mg/kg Cs, 1 mg/kg Cs (d1-3) followed by 5 or 7.5 mg/kg LAB (d4-6), or 5% dextrose (D5W). Day 4, tissues were collected from 7 mice/gp, homogenized and used to determine Log10 cfu/g (Lcfu) by plating on Sabouraud's agar, and to assess drug concentration in spleen, kidneys and heart using a Candida albicans agar bioassay. Another 7 mice/gp received 6 days of treatment and were monitored for morbidity for 21 days. Results: C. parapsilosis MIC for LAB was 0.5 ug/ml and for Cs, 3 ug/ml. Survival with either dose of LAB alone (100%) or combined with Cs (87% for 5 mg/kg LAB+Cs and 100% for 7.5 mg/kg LAB+Cs) was significantly better (p< 0.05) than with Cs alone or Cs prior to LAB (14%). D5W mice all died. Fungal burden (Lcfu) for 7.5 mg/kg LAB, with or without Cs, was 5.1-5.3 (spleen), 5.0-5.4 (kidneys), 4.5-4.7 (liver), 5.6-6.4 (heart), 4.4-4.7 (brain). These values were significantly lower (p<0.05) than those for Cs or D5W (spleen 6.6 and 7.1; kidneys 6.3 and 6.9; liver 5.1 and 5.9; heart 7.3 and 7.8; brain 5.2 and 5.3). Mean tissue concentrations were similar for 5 or 7.5 mg/kg LAB (spleen, 1576-1665 ug/g; kidneys, 17-21 ug/g; heart, 3.2-4.5 ug/g) with Cs levels less than 2.5 ug/g in these tissues. Conclusion: No synergy was observed with the combination of LAB and Cs for the treatment of C. parapsilosis infection since LAB alone was as effective as LAB plus Cs in prolonging survival and decreasing tissue fungal burden. Animals initially treated with Cs for 3 days could not be rescued by switching treatment to LAB.