Table 2

Clinical Efficacy of Inhaled Amphotericin B

Investigators	Study Design/Primary Endpoints	Patients	Primary Findings

Dubois, et al[10]	Prospective, single center, single agent
	
	Dose/duration
	• 3 mL of 10 mg/mL solution delivered via Respirgard II nebulizer using oxygen at a flow rate of 6 L/min
	• Amphotericin inhalations discontinued if granulocytes rose to > 500/mL, Scr rose to over 1.0 mg/mL, there was evidence of a systemic reaction (hypotension, tachycardia, rigors), or if IV amphotericin therapy was initiated
	
	Primary endpoint
	• Assessment of respiratory effects of inhaled amphotericin B
	  • oxygen saturation monitored throughout therapy
	  • peak flow values measured before and after therapy
	  • cough and dyspnea rated by patients using Borg scale
		18 patients enrolled in study (mean of 4.98 treatment courses/patient)
		• Inclusion criteria
		  • granulocytopenia (< 500 granulocytes/mm^3) projected to last > 2 weeks
		  • expected life span >2 weeks
		  • ability to give informed consent
		  • ≥18 years of age
		  • lack of fever
		• Exclusion criteria
		  • prior history of fungal infection
		  • history of severe asthma
		  • treatment with amphotericin B at time of possible enrollment
		  • history of anaphylactic response to amphotericin B
		  • Scr > 2mg/dL
		  • refusal to sign informed consent
		• 18 bone marrow transplant patients
		• 2 patients that underwent leukemic induction therapy
		• Patients stopped therapy, due to
		  • granulocytes > 500/mL
		  • vomiting
		  • became comatose
		  • mucositis
			• The mean arterial oxygen saturation level was 97% at onset and 98% at the end of therapy, with the largest drop being 4%
			• Mean peak flow dropped from 539 L/min before therapy to 520 L/min after ($p < 0.001$)
			  • 9 instances of clinically significant drop in peak flow (drop of 20% or more), four of which occurred in asthmatic patients
			  • significant drop in peak flow with 21% of treatments given to asthmatic patients vs 4.4% of patients without asthma
			• Amphotericin therapy associated with dyspnea and cough
			  • mean Borg scale rating for cough went from 0.4 ± 0.7 before therapy to 0.9 ± 1.5 after ($p < 0.001$)
			  • cough increased by more than 2 Borg descriptors for 9 treatments
			  • mean Borg scale rating for dyspnea went from 0.3 ± 0.7 to 0.7 ± 1.2 after treatment ($p < 0.001$)
			  • dyspnea increased by more than two Borg descriptors in three cases

Rijnders, et al[11]	Randomized, double-blind, placebo-controlled trial
	
	Dose/duration
	• 2.5 mL of a 5 mg/mL solution of liposomal amphotericin B (AmBisome®)
	• Placebo
	• Nebulized for 30 minutes/day on two consecutive days per week until neutrophil recovery (ANC > 300 cells/mm3), with a maximum of 12 inhalations per neutropenic episode
	• Nebulization performed with an adaptive aerosol delivery system (Halolite AAD or ProDose AAD)
	
	Primary endpoint
	• Occurrence of invasive pulmonary aspergillosis according to European Organization for Research and the Treatment of Cancer-Mycoses Study Group (EORTC-MSG) definitions
	
	Other endpoints
	• Overall mortality
	• Invasive pulmonary aspergillosis-related mortality
	" Safety
		271 patients enrolled in the study (139 received amphotericin, 132 received placebo)
		
		• Inclusion criteria
		  • adult with hematologic disease hospitalized at Erasmus Medical Center in the Netherlands
		  • had to start chemotherapy within seven days after enrollment with anticipated duration of neutropenia (ANC < 500 cells/mm^3) for ≥ 10 days
		  • received prophylactic fluconazole
		
		• Exclusion criteria
		  • evidence of fungal infection in lung or sinuses at onset of trial
		  • unable to use nebulizer
		  • expected survival < 3 months
		  • previous intolerance to amphotericin B
		
		• Hematologic and clinical characteristics between the two treatment groups was balanced
			• Development of invasive pulmonary aspergillosis occurred in 4% of amphotericin-treated patients and 14% of placebo patients ($p = 0.005$)
			• Within 28 days of neutrophil recovery, seven patients died from the amphotericin group (none were aspergillosus-related deaths). In the placebo group, six patients died (one was aspergillosis-related).
			• Median Scr levels after the last inhalation were not greater than the baseline level in amphotericin-treated patients.
			• Treatment was discontinued if the patient was too weak to use the aerosol system or if the patient experienced technical problems with the system.
			• Aerosolized amphotericin was generally well tolerated. Coughing during inhalation occurred in 16 patients of the amphotericin group and 1 patient of the placebo group ($p = 0.02$).
			• No serious adverse effects or systemic toxicities were reported.