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Liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients

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Liposomal amphotercin B was compared with conventional amphotericin B for empirical antifungal therapy in febrile neutropenic patients in a randomized, double-blind, multicentre trial. Using a composite end-point, the two drugs were equivalent in overall efficacy. However, the liposomal amphotericin B treatment group had fewer proven fungal infections, fewer infusion-related side effects and less nephrotoxicity. Patient data from that study were analysed to compare the pharmacoeconomics of liposomal versus conventional amphotericin B therapy. Itemized billing data from 414 patients were collected and analysed. Hospital costs from first dose were significantly higher for all patients who received liposomal amphotericin B ($48 962 versus $43 183, $P = 0.02$). However, hospital costs were very sensitive to the cost of the study medication ($39 648 versus $43 048, when acquisition costs are not included, $P = 0.4$). Using decision analysis models and sensitivity analyses to vary the cost of study medications and risk of nephrotoxicity, the break-even points for the cost of liposomal therapy were calculated to range from $72 to $87 per 50 mg for all patients, and $83 to $112 per 50 mg in allogeneic bone marrow transplant patients. Therefore, the drug acquisition costs and the risk of nephrotoxicity are important factors in determining the cost-effectiveness of liposomal amphotericin B as empirical therapy in persistently febrile neutropenic patients. In a recent randomized double-blind study comparing liposomal amphotericin B at 3 or 5 mg/kg/day with amphotericin B lipid complex (ABLC) 5 mg/kg/day as empirical antifungal treatment in patients with febrile neutropenia, liposomal amphotericin B was associated with less toxicity than ABLC, both in terms of infusion-related reactions and nephrotoxicity. The incidence of study drug discontinuation due to toxicity was: liposomal amphotericin B 3 mg/kg/day, 14%; liposomal amphotericin B 5 mg/kg/day, 15%; and ABLC, 42% ($P < 0.001$).

Introduction

Invasive fungal infections are difficult to diagnose and neutropenic patients with refractory fever are frequently commenced on empirical antifungal treatment. Amphotericin B is administered as empirical therapy to such patients; however, its use is associated with severe toxicities.[1] A study published by Walsh *et al.*[2] presented the results of a comparative trial of liposomal versus conventional amphotericin B for empirical treatment of patients with fever and neutropenia. This investigation found that based on efficacy, liposomal amphotericin B at a dose of 3 mg/kg/day was equivalent to conventional amphotericin B 0.6 mg/kg/day as empirical therapy, but was associated with significantly fewer side effects.

High-risk patient population

Allogeneic stem cell transplant recipients are considered to be high-risk patients susceptible to fungal infection and nephrotoxicity. A subset of 103 patients from the Walsh study[2] that received allogeneic stem cell transplantations were analysed separately.

The high-risk groups were well balanced in terms of gender distribution, race distribution and mean age (Table 1). The diagnoses of the patients were also well balanced, with a higher number of leukaemic patients undergoing allogeneic transplantation. The mean baseline creatinine concentrations were equivalent and normal in both groups. A number of patients received fluconazole prophylaxis before the initiation of empirical therapy.

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Table 1. Characteristics of patients in the allogeneic transplant groups that were included in the empirical therapy clinical trial

Characteristic	LAB ($n = 53$)	Amphotericin B ($n = 50$)
Gender (%)		
male	62	70
female	38	30
Race (%)		
white	87	78
black	4	18
other	9	4
Age, years [mean (range)]	34 (34–58)	34 (3–56)
Diagnosis (%)		
acute leukaemia	40	36
chronic leukaemia	30	26
myelodysplasia/refractory anaemia	4	8
myeloma	8	6
other	5	12
Creatinine (μg/L; mean baseline)	75	81
Fluconazole (%) prophylaxis	64	50

LAB, liposomal amphotericin B.

Table 2. Nephrotoxicity in allogeneic bone marrow transplant patients receiving either liposomal amphotericin B 3 mg/kg/day or conventional amphotericin B 0.6 mg/kg/day as empirical therapy

Variable	LAB	Amphotericin B	*P*
2× baseline creatinine value	32%	66%	<0.001
Haemodialysis required	1	5	0.08
Hypokalaemia ($K^+ < 3$ meq/L)	19%	14%	0.51
Dose reductions	17%	60%	<0.001

LAB, liposomal amphotericin B.

Fluconazole prophylaxis was not an exclusion factor for the trial.

Toxicity results

The comparative toxicity data in the allogeneic stem cell transplant patients are presented in Table 2. Nephrotoxicity, defined as a doubling of baseline creatinine, occurred in one-third of the patients receiving liposomal amphotericin B, but was significantly greater in the patients on amphotericin B. These results show that when treating allogeneic stem cell transplant recipients empirically with conventional amphotericin B, *c.* 70% of the patients suffer nephrotoxicity. The number who required haemodialysis included five patients on conventional amphotericin B compared with one patient on liposomal amphotericin B. Although this difference did not reach significance, it corroborates the evidence that liposomal amphotericin B is significantly less nephrotoxic than conventional amphotericin B. Further evidence to support the comparative safety profile of liposomal amphotericin B comes from the number of patients that required dose reductions due to adverse side effects. Dose reductions occurred in 60% of patients in the conventional amphotericin B group, compared with 17% of patients in the liposomal amphotericin B group ($P < 0.001$). This analysis did not find any significant differences in hepatotoxicity between the liposomal amphotericin B and amphotericin B treatment groups.

Breakthrough fungal infections

Empirical antifungal therapy is employed when a patient has a fever that does not respond to antibiotics, indicating possible sub-clinical fungal infection. When a proven

fungal infection becomes evident, it is clear that empirical antifungal therapy has failed. Consequently, it is important to consider the breakthrough fungal infections when evaluating the benefit of an empirical therapy. There were seven (14%) microbiologically proven breakthrough fungal infections in the amphotericin B treatment arm and only one (1.9%) breakthrough infection in the liposomal amphotericin B treatment group; this difference is statistically significant ($P < 0.05$). All infections were reviewed and confirmed by an independent, blinded reviewer. Of the seven infections that occurred in the amphotericin B arm, two were *Aspergillus* spp., three were *Candida* spp. and two were unspecified fungi. The majority of breakthrough infections occurred in patients not receiving fluconazole prophylaxis. Importantly, five of the seven infections occurred in patients that had the amphotericin B dose reduced due to toxicity. The single infection that occurred in the liposomal amphotericin B arm was identified as a zygomycosis in a patient that did not receive prophylaxis and did not have any dose reduction. Thus, this retrospective analysis of allogeneic transplant patients confirmed that empirical therapy with liposomal amphotericin B was associated with significantly less nephrotoxicity and fewer breakthrough fungal infections than amphotericin B therapy.

Pharmacoeconomic analysis of liposomal amphotericin B empirical therapy

The overall pharmacoeconomic impact of liposomal amphotericin B compared with amphotericin B as empirical therapy in persistently febrile neutropenic patients, and in the subset of allogeneic transplant patients, was evaluated.[4] This study highlights the cost of nephrotoxicity in this setting. Of the patients in the Walsh study, 414 had hospital billing data available for analysis; 56 were allogeneic transplant patients. The populations remained comparable with regard to age, gender distribution and the proportion of high-risk patients (Table 3) and were balanced with respect to autologous and allogeneic transplantation. One objective of the study was to determine whether there was any difference in cost-effectiveness of liposomal amphotericin B versus amphotericin B for high-risk patients. This retrospective analysis included all costs from the first dose of empirical therapy until discharge. All data come from the randomized double-blind trial. Physicians were blinded to the study medication and any differences in costs reflect patient management.

Effect of nephrotoxicity on costs

One of the most important findings of the study was the cost of nephrotoxicity. The question of whether nephrotoxicity is a true factor, or a surrogate marker for more ill patients, does not need to be resolved for the purposes of the study. Nephrotoxicity in the trial was defined as a doubling of the baseline of creatinine. Of patients included in the pharmacoeconomic study, 18.7% of those receiving liposomal amphotericin B had renal toxicity compared with 66.3% of patients in the conventional amphotericin B arm. Patients that developed nephrotoxicity had significantly longer hospitalizations compared with patients without nephrotoxicity (22.8 versus 15.8 days, $P < 0.001$). Furthermore, total hospital costs were significantly higher ($59 621 versus $34 415, $P < 0.001$). These results clearly corroborate the findings published in a study by Wingard *et al.*[3] reporting that 61% of allogeneic bone marrow transplant patients on amphotericin B for suspected or proven aspergillosis had a doubling of baseline creatinine. This group was also at significantly greater risk for haemodialysis compared with non-transplant patients.

Economic analysis

The decision analysis model excludes the acquisition costs of the drugs being evaluated. The number of patients in each of the test groups or arms of the study can be segregated into the number with nephrotoxicity and the number without nephrotoxicity. By multiplying the average hospitalization cost per patient by the number of patients in that category, one can arrive at the total and average hospital costs per patient in each arm of the trial. As more patients in the amphotericin B arm had more nephrotoxicity, the average cost per patient in this arm was $3781 greater than in the liposomal amphotericin B arm. When the same calculations are computed for the allogeneic bone marrow transplant patients, this difference in cost increases to $5506.

Since these costs do not include the cost of the treatment drug, one must ask, 'Will $3781 buy an average course of treatment of liposomal amphotericin B?' In order to answer this question one must first make an assumption of the fixed acquisition cost of conventional amphotericin B, which in this case was $5 per 50 mg. Now one assumes differing acquisition costs for a vial of 50 mg of liposomal amphotericin B, and calculates where that price function line crosses the price line for the treatment with amphotericin B. In this example the liposomal amphotericin B price was calculated to be $87 per 50 mg vial.

A similar analysis was performed for the allogeneic transplant recipients, and the difference in cost between the two arms of the study was $5506. Again, by varying the hypothetical cost of liposomal amphotericin B, the break-even point now was calculated to be $112 per 50 mg vial. It must be remembered that these figures include tangible monetary costs only.

Comparison of liposomal amphotericin B and Abelcet in empirical therapy

The only trial comparing two lipid formulations of amphotericin B in a double-blind, randomized prospective fashion

Table 3. Patient characteristics by treatment group for the pharmacoeconomic study

Characteristic	LAB ($n = 206$)	Amphotericin B ($n = 208$)
Mean age, years	40.4	41.7
Gender, male (%)	48	53
Stratification (%)		
high risk	29	26
low risk	71	74
Autologous BMT (%)	36	39
Allogeneic BMT (%)	14	13

LAB, liposomal amphotericin B; BMT, bone marrow transplant.

was published recently by Wingard *et al*.[3] The main objective of this study was to compare the safety of these two drug formulations. With 78–85 patients per arm, the trial was not powered to identify efficacy differences, although efficacy data were collected for each treatment arm. Liposomal amphotericin B was given at 3 mg/kg/day (recommended dose) and 5 mg/kg/day for comparison purposes. Amphotericin B lipid complex (ABLC) was given at 5 mg/kg/day, which is the dose recommended by the manufacturer.

Patients had to be at least 2 years old with a neutrophil count $<0.5 \times 10^9$ cells/L. Patients also had to have a temperature of $\geq$38°C that had not responded to 72 h of broad-spectrum antibiotic therapy. Patients were excluded if they had serum creatinine values > 300 μg/L, or liver disease as defined by transaminases greater than 10 times the upper limit of normal, or bilirubin or alkaline phosphatase greater than five times the upper limit of normal. Patients with active fungal infection or a past history of fungal or bacterial infection were excluded. Patients who had received more than two doses of any amphotericin B preparation within the last 10 days were not eligible for the study.

Study drugs were administered once daily over a period of 2 h. Therapy was continued until neutrophil count had recovered to $>0.5 \times 10^9$ cells/L or for up to 3 days after recovery, with a maximum of 42 days treatment. During the first administration of study drug, no pre-medications were allowed, although they could be used thereafter. Patients were withdrawn from the study if there was unacceptable toxicity, if the patient or physician decided to withdraw, or if the patient was started on an alternative antifungal therapy for probable or proven fungal infection.

Success was defined by all of the following:

(i) survival for 7 days post administration of study drug;
(ii) resolution of fever during the neutropenic period;
(iii) resolution of any microbiologically confirmed study-entry fungal infection;
(iv) no proven or presumed emergent fungal infection while on study drug or within 7 days after study drug;
(v) no premature discontinuation of study drug due to toxicity.

Of patients enrolled, at least one dose of study drug was received by 85 patients in the liposomal amphotericin B 3 mg/kg arm, 81 patients in the liposomal amphotericin B 5 mg/kg arm and 78 patients in the ABLC 5 mg/kg arm. Most of the patients were low risk, and the groups were balanced with regard to age, gender and race.

Infusion-related side effects

One of the main study objectives was to compare infusion-related side effects on day 1, as well as other safety variables, particularly nephrotoxicity. There was a significantly lower incidence of chills and rigors, or fever on the first day of study drug in the groups receiving liposomal amphotericin B (Table 4). During later infusions, chills and rigors were significantly greater for the ABLC arm than either liposomal amphotericin B treatment groups. Use of medications such as paracetamol, diphenhydramine, pethidine and hydrocortisone to treat infusion-related reactions was significantly lower in the liposomal amphotericin B groups compared with the ABLC group ($P < 0.001$). Drug was withdrawn due to infusion-related reactions in two patients in the liposomal amphotericin B 3 mg/kg/day group, five patients in the liposomal amphotericin B 5 mg/kg/day group and nine patients in the ABLC 5 mg/kg/day group (not significant).

Other toxicities

Nephrotoxicity, defined as a doubling of the baseline creatinine, occurred in *c.* 15% of the liposomal amphotericin B patients compared with 42% of ABLC patients ($P \leq 0.001$; Table 5). Almost 18% of the ABLC patients

Table 4. Incidence of infusion-related reactions on day 1 among patients in the three treatment groups

Infusion-related reaction	LAB (3 mg/kg/day) (n = 85) (%)	LAB (5 mg/kg/day) (n = 81) (%)	ABCL (5 mg/kg/day) (n = 78) (%)
Chills/rigors	18.8	23.5	79.5
Fever: ⩾1°C increase	23.5	19.8	57.7
Nausea	10.6	8.6	11.5
Vomiting	5.9	6.2	14.1
Other reactions[a]	18.8	25.9	41.0
Total	51.8	48.1	88.5

LAB, liposomal amphotericin B; ABLC, amphotericin B lipid complex.
[a]Included pain, hypertension, tachycardia, chest pain, vasodilation and hypotension.

Table 5. Incidence of nephrotoxicity among patients in the three treatment groups

Variable	LAB (3 mg/kg/day) (n = 85) (%)	LAB (5 mg/kg/day) (n = 81) (%)	ABCL (5 mg/kg/day) (n = 78) (%)
Nephrotoxicity (%)			
2× baseline creatinine	14.1	14.8	42.3
Change in creatinine value median (range, μg/L)	30 (0–470)	20 (–10–210)	70 (0–530)
Peak creatinine (%) >250 μg/L	7.1	3.7	17.9

LAB, liposomal amphotericin B; ABLC, amphotericin B lipid complex.

had a peak creatinine level >250 μg/L compared with *c.* 5% of patients in the liposomal amphotericin B groups.

Hepatotoxicity, as determined by raised serum transaminase levels and bilirubin levels, occurred in 11.5% of all patients. There were no statistically significant differences between any of the treatment groups in terms of hepatotoxicity.

Study drug was withdrawn due to toxicity in 11 patients in the liposomal amphotericin B 3 mg/kg/day group, 10 patients in the liposomal amphotericin B 5 mg/kg/day group and 25 patients in the ABLC 5 mg/kg/day group ($P \leqslant 0.01$, for both liposomal amphotericin B treatment groups compared with ABLC group).

Efficacy

There were no significant statistical differences between the three groups. Actual response rates were 40–42% for liposomal amphotericin B and 33% for ABLC. One patient each in the liposomal amphotericin B 3 mg/kg/day and ABLC groups had a baseline, persistent or progressive fungal infection. Breakthrough fungal infections occurred in three patients in each group, as well as in two patients in the liposomal amphotericin B 5 mg/kg/day group. Death related to fungal infection occurred in one patient in the liposomal amphotericin B 3 mg/kg/day group compared with no fungal-related deaths in the liposomal amphotericin B 5 mg/kg/day group, and three in the ABLC group.

Conclusion

In conclusion, this study showed that, based on infusion-related reactions and nephrotoxicity, liposomal amphotericin B given at 3 or 5 mg/kg/day was significantly less toxic than ABLC 5 mg/kg/day.

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