An open study of the comparative efficacy and safety of caspofungin and liposomal amphotericin B in treating invasive fungal infections or febrile neutropenia in patients with haematological malignancy

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In a clinical non-trial setting, the efficacy and safety of caspofungin was compared with liposomal amphotericin B for the management of febrile neutropenia or invasive fungal infections in 73 episodes in patients with haematological malignancy. There were fewer episodes of drug toxicity with caspofungin than liposomal amphotericin B (58.3 vs 83.7 %, $P=0.02$). The favourable response rate for episodes of febrile neutropenia treated with caspofungin or liposomal amphotericin B was similar at 37.5 and 53.8 %, respectively, but more breakthrough fungal infections occurred with caspofungin than with liposomal amphotericin B (33.3 vs 0 %, $P<0.05$) in these patients who did not receive antifungal prophylaxis. None of four episodes of candidaemia or hepatosplenic candidiasis responded to caspofungin compared with three of four episodes treated with liposomal amphotericin B. Mortality was significantly higher with caspofungin treatment compared with liposomal amphotericin B (6/24 vs 2/49, $P=0.01$), mainly due to an excess of fungal infections ($P=0.04$). Caspofungin treatment was a significant independent predictor of mortality [odds ratio = 7.6 (95 % confidence interval 1.2–45.5)] when sepsis severity, prolonged neutropenia and length of antifungal therapy were considered in a multiple logistic regression model. In clinical practice, there is a suggestion that caspofungin may not be as effective as liposomal amphotericin B in preventing breakthrough invasive fungal infections in febrile neutropenia or in preventing fungus-related deaths. Because of the potential biases in this observational study, these preliminary findings should be interpreted with caution and clarified with a larger cohort of patients.

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INTRODUCTION

Invasive fungal infections (IFIs) are the most frequently encountered infective complications resulting in the highest mortality among patients with haematological malignancy (Karthaus & Cornely, 2005; Lin *et al.*, 2001). Up to 20 % of episodes of febrile neutropenia are caused by IFIs (EORTC International Antimicrobial Therapy Cooperative Group,

1989). *Candida* species occur in approximately the same proportion as *Aspergillus* species. However, the contribution from *Candida non-albicans* species, *Aspergillus terreus* and moulds other than *Aspergillus* species is increasing globally and is dependent on institutional micro-ecology (Karthaus & Cornely, 2005). As the outcome of IFIs is related in part to swift and early diagnosis linked to effective antifungal therapy (Caillot *et al.*, 1997) to which suspected or proven organisms are likely to be susceptible, the initial choice of an antifungal drug is important.

Liposomal amphotericin B (AmBisome) is one of three lipid formulations of amphotericin B that has been advocated

Abbreviations: ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CT, computed tomography; IFI, invasive fungal infection; IPA, invasive pulmonary aspergillosis; NF, neutropenic fever unresponsive to broad-spectrum antibiotics.

as the current gold-standard therapy for IFIs in view of its enhanced activity and reduced toxicity compared with conventional amphotericin B (Ostrosky-Zeichner *et al.*, 2003). Issues of high drug-acquisition costs, notable, though reduced, systemic and renal toxicities, and the persistently high mortalities despite treatment, have driven the development of alternative antifungal drugs, particularly the echinocandin caspofungin. This drug is licensed for empirical therapy of neutropenic fever, candidaemia and for salvage treatment of invasive aspergillosis (Maertens *et al.*, 2004; Mora-Duarte *et al.*, 2002; Walsh *et al.*, 2004).

Prior to 2002, liposomal amphotericin B was the major licensed approved antifungal drug available to treat neutropenic fever or an invasive fungal infection. Caspofungin was added to Tawam Hospital's formulary as an alternative treatment drug in 2002. Physicians had the option of using caspofungin or liposomal amphotericin B. This paper analyses the indications, responses, mortality and toxicity for each drug used in a real-time, non-trial setting since 2002.

METHODS

Study design. This study comprised an open, comparative, retrospective, case-centred analysis of patients who had been prescribed caspofungin or liposomal amphotericin B, and was approved by the Al-Ain Medical District Human Research Ethics Committee.

Patients. Patients admitted to Tawam Hospital, the tertiary care oncology centre for the United Arab Emirates, with a diagnosis of acute haematological malignancy received standard induction or consolidation chemotherapy following international guidelines (Coiffier *et al.*, 2002; Farag *et al.*, 2005; Medical Research Council Working Party on Leukemia in Adults, 2006). Prophylactic antibiotics and antifungals were not used. Those patients with prolonged neutropenia or who developed an invasive fungal infection received haematopoietic growth factors. Patients who developed bacterial-culture-negative, target-organ-negative neutropenic fever unresponsive to broad-spectrum antibiotics (NF) or who had an IFI were given either caspofungin or liposomal amphotericin B at the discretion of the treating physician. In keeping with antimicrobial guidelines in use in Tawam Hospital, no patient received antifungal drug prophylaxis unless there was a previous episode of IFI.

Drug administration. Caspofungin was given at an initial loading dose of 70 mg intravenously, followed by 50 mg daily. Liposomal amphotericin B was given at a dose of 3 mg kg⁻¹ per day for NF or 5 mg kg⁻¹ per day for invasive pulmonary aspergillosis (IPA), candidaemia or hepatosplenic candidiasis. The physician could dose-escalate AmBisome to up to 10 mg kg⁻¹ per day for progressive fungal disease. Guidelines indicated that treatment was continued until neutropenia and fever had resolved and the drug had been administered for at least 10 days for NF. For IFI, treatment was given until there was a satisfactory response, recovery of neutropenia and at least 14 days of intravenous treatment had been given and the patient was considered fit for discharge. Orally administered voriconazole was given to patients with a satisfactory response for a further 14 days. Patients who developed progression of their IFI or whose NF did not respond had their initial antifungal drug changed to an alternative antifungal treatment. This was at the discretion of the treating physician. Generally, for patients receiving caspofungin, liposomal amphotericin B was substituted and vice versa. For patients who had cardiovascular instability or who were otherwise judged highly septic, combination therapy was given (see Table 6).

Definitions and measurements

Neutropenic fever. NF was defined as a neutrophil count of $<0.5 \times 10^9 \text{ l}^{-1}$ with a temperature of $\geq 38^\circ\text{C}$ (Hughes *et al.*, 2002) where there was neither clinical focal infection nor positive blood cultures for pathogenic bacterial organisms on two occasions.

Invasive fungal infection. IFI was defined according to EORTC/MSG criteria (Ascioglu *et al.*, 2002) with modification for IPA. A probable case of IPA was therefore diagnosed if a high-resolution computed tomography (CT) scan demonstrated a halo sign with one or more host factor criteria and two or more minor criteria. A halo sign is widely accepted as pathognomonic for IPA in this patient setting (Kami *et al.*, 2002).

NF response. Both the unabridged five-point criteria as used by Walsh and others (Walsh *et al.*, 2004) and a modification were used. The modification was to allow for resolution of fever outside the period of neutropenia but before the end of the study drug administration.

IPA or hepatosplenic candidiasis response. This was based on previous literature citations (Maertens *et al.*, 2004). A complete response was resolution of all clinical and radiological features (a). A partial response was meaningful improvement of clinical features and ≥ 50 to $<100\%$ improvement of the radiographical score (b). Stable disease was neither improvement nor worsening of the clinical features and radiographical score (c). Progressive disease was worsening of the radiographical score and clinical features necessitating administering an alternative antifungal drug or resulting in death (d). (a) or (b) was considered to be a response to treatment; (c) or (d) was a failure. Outcome was measured at the time of discharge and again at a 1 month follow-up after hospital discharge (modified response).

Candidaemia response. This was resolution of all clinical signs with two or more consecutive negative blood cultures for *Candida* species. Failure was no improvement or worsening of clinical signs with persistence or relapse of positive blood cultures, resulting in a change in antifungal therapy or death.

Radiographical scores. It was hypothesized that each *Aspergillus* lesion had an ovoid shape. Each lesion was measured in the two longest axes at the CT section where the lesion was seen to be biggest. The measure of the lesion height, along the z axis, was obtained by using jointed CT sections. The calculated volume in cm³ of each lesion was obtained using the following formula: $\text{volume} = [(\text{height} \times \text{length} \times \text{width}) \times 3.1416]/6$. For several *Aspergillus* lesions, the total volume was calculated by the addition of each volume (Calliot *et al.*, 2001).

Toxicity. Toxicity due to, or possibly due to, the study drug was measured according to universal clinical toxicity criteria definitions for liver, creatinine, potassium and infusion-related chills/rigors. At least 1 day of drug toxicity was recorded as a toxic event.

Outcome measurements. The primary outcome measurements were: (i) all causes of mortality within 7 days of completing the antifungal drug treatment; (ii) response to treatment; and (iii) toxicity. This primary analysis was performed for patients receiving the drug for the first time during their hospital admission and who had not received an antifungal drug for at least 1 month previously. Secondary outcome measurements included all antifungal drug administrations during each hospital admission.

Statistical methods. Standard descriptive statistics, including means, medians and frequencies, were used to describe the presentation and outcome features of the two treatment groups. Percentages were compared between the groups using a χ^2 or Fisher's exact test as appropriate. Other variables were tested using independent *t* tests

or the non-parametric Mann–Whitney U test. An exploratory multivariate analysis was used to determine whether any differences in mortality between therapies could be explained by differing prognostic profiles. The exploratory nature of this logistic regression analysis is emphasized, given that the number of events (eight deaths) was limited and that the true independence of the 73 episodes used may be questioned.

RESULTS

From April 2002 to November 2004, there were 97 antifungal treatment episodes with caspofungin and/or liposomal amphotericin B. Seventy-three of these were distinct treatment episodes with monotherapy of caspofungin or liposomal amphotericin B. Fifty of these 73 were for first exposure to caspofungin or liposomal amphotericin B and 23 were a second or subsequent monotherapy treatment episode, 18 of which had received systemic antifungal treatment with one of the drugs more than 1 month previously. Another 19 episodes were of sequential monotherapy in patients who had failed treatment with the initial antifungal drug and were then given the alternative drug immediately for the same treatment episode. Another five episodes involved initial combination therapy with caspofungin plus liposomal amphotericin B. The focus of this analysis is on the 73 distinct episodes as defined above.

The demographics and haematological characteristics of the 73 treatment episodes are detailed in Table 1. There were 24 episodes with caspofungin treatment and 49 with liposomal amphotericin B treatment. No significant differences between the two drug treatment groups were seen apart from the Karnovsky scale, which was significantly lower ($P < 0.01$) in patients treated with caspofungin. There were also significantly more diagnoses ($P = 0.009$) of haematological diseases other than acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL) in the episodes treated with caspofungin.

The indications for antifungal drug therapy are shown in Table 2. The 23 episodes of neutropenic fever, 40 episodes of IFI and 10 episodes of secondary prophylaxis were similarly distributed between the two drug treatments. However, there were more cases of IPA treated with liposomal amphotericin B and slightly more cases of candidal and other IFIs treated with caspofungin.

NF responses

The mean ($\pm$ SD) duration of drug treatment was 10 ± 7.2 days for caspofungin compared with 8.6 ± 4.9 days for liposomal amphotericin B ($P = 0.6$). The overall response rate (Table 2) was similar for the two drug treatments, even

Table 1. Characteristics of patients and treatment episodes

Episode characteristics are given as the number of episodes, with the percentage in parentheses, unless otherwise indicated.

Patient characteristics	Caspofungin	AmBisome	P value
No. of patients	23	34	
Age (mean years $\pm$ SD)	38.7 ± 16.0	33.1 ± 11.3	
Weight (mean kg $\pm$ SD)	66.6 ± 14.0	70 ± 16.8	
Sex ratio (male:female)	16:7	27:7	
Episode characteristics			
Distinct antifungal drug treatment episodes	24	49	
Admission (mean Karnovsky $\pm$ SD)	77.7 ± 21.8	90.7 ± 7.8	0.002
Co-morbidity	12 (50.0)	23 (46.9)	0.81
Diagnosis of malignancy:			
Acute myeloid leukaemia	10 (41.7)	31 (63.3)	0.009
Acute lymphocytic leukaemia	6 (25.0)	15 (30.6)	
Other	8* (33.3)	3† (6.1)	
Chemotherapy received:			
Induction	17 (70.8)	31 (63.3)	0.50
Consolidation	4 (16.7)	14 (28.6)	
Supportive	3 (12.5)	4 (8.2)	
Persistent disease at discharge	7/19 (36.8)	11/45 (24.4)	0.31
Associated bacteraemia	7 (29.2)	19 (38.8)	0.42
Severe sepsis/septic shock at start of antifungal treatment	2 (8.3)	3 (6.1)	1.00
Median of neutropenic days on antifungal treatment (range)	6 (0–28)	7 (0–29)	0.28

*Comprising three non-Hodgkin's lymphoma patients, two aplastic anaemia patients, one bone marrow allograft plus graft versus host disease patient, one pre-B-cell lymphoblastic lymphoma patient and one hairy cell leukaemia patient.

†Comprising one aplastic patient, one Hodgkin's lymphoma patient and one Burkitt's lymphoma patient.

Table 2. Indications for antifungal drug treatment and outcome

Response rates were calculated as responses/number episodes assessable. Percentage values are shown in parentheses.

Indication/outcome	Caspofungin (n = 24)	AmBisome (n = 49)	P value
Neutropenic fever			
No. of episodes	9	14	0.44
Favourable response	3/8† (37.5)	7/12‡ (58.3)	0.65
Modified favourable response	6/9 (66.7)	9/12‡ (75.0)	1.00
Invasive fungal infections			
Pulmonary aspergillosis			
No. of episodes	4	20	0.04
Favourable response	2/4 (50.0)	11/20 (55.0)	
Modified favourable response	3/4 (75.0)	12/18 (66.7)	
Candidaemia			
No. of episodes	2	1	0.25
Favourable response	0/2 (0)	1/1 (100)	
Modified favourable response	0/2 (0)	1/1 (100)	
Hepatosplenic candidiasis			
No. of episodes	2	3	1.00
Favourable response	0/2 (0)	2/3 (66.7)	
Modified favourable response	0/2 (0)	2/3 (66.7)	
Other invasive fungal infections*			
No. of episodes	5	3	0.10
Favourable response	2/4§ (50.0)	1/2§ (50.0)	
Modified favourable response	2/4 (50.0)	1/2 (50.0)	
Total invasive fungal infections			
No. of episodes	13	27	0.94
Favourable response	4/12 (33.3)	15/26 (57.7)	0.16
Modified favourable response	5/12 (41.7)	15/23 (65.2)	0.18
Secondary prophylaxis			
Successful episodes	1/2 (50.0)	7/8 (87.5)	0.37

*These comprised (no. of cases in parentheses): invasive fungal sinusitis (1), buccal fungal infection (1), uncertain IFI lung (2) and IPA with *C. tropicalis* fungemia (1) in the caspofungin-treated group; and invasive sinus aspergillosis (2) and uncertain IFI in the lung (1) in the AmBisome-treated group. Reasons for non-assessability were: †not neutropenic; ‡complicated by Gram-negative bacteraemia or bacterial pneumonia; §did not have an IFI.

when the five-point composite score was modified to allow for late defervescence. Reasons for the treatment failures in each group (Table 3) included three episodes of breakthrough IFI (one each of IPA, cryptococcosis and candidaemia), all of which occurred under caspofungin treatment ($P=0.047$). Two instances of severe drug toxicity were seen with liposomal amphotericin B and were due to hyperbilirubinaemia in both instances. One episode in each treatment group resulted in death due to underlying malignant disease. One episode treated with caspofungin and two receiving liposomal amphotericin B, respectively, failed to defervesce during neutropenia but did so after resolution of neutropenia.

The mean ($\pm$ SD) time to defervescence was 4.5 ± 2.5 and 6 ± 3.4 days ($P=0.35$) for episodes treated with caspofungin and liposomal amphotericin B, respectively.

Mean C-reactive protein values documented at weekly intervals did not differ between the two treatment groups (data not shown).

IFI responses

Thirteen of the 40 episodes of IFI were treated with caspofungin and 27 were treated with liposomal amphotericin B (Table 3). The proportion of overall favourable responses was slightly higher in the liposomal amphotericin B treatment group (57.7 vs 33.3 %, respectively; $P=0.16$). The response rate for IPA was similar for caspofungin and liposomal amphotericin B (50.0 and 55.0 %, respectively). However, none of the four episodes of candidaemia and hepatosplenic candidiasis responded to treatment with caspofungin, whilst three of the four patients treated with

Table 3. Details of the failures in the treatment of NF

CTC, clinical toxicity criteria grade.

Failure to:	Caspofungin	AmBisome	Details (no. of cases)
Treat baseline infection	—	—	None
Prevent breakthrough IFI ($P=0.047$)	3	0	IPA (1), cryptococcosis (1), <i>Candida non-albicans</i> (1)
Survive >7 days	1	1	Both underlying haematological disease
Complete treatment due to drug toxicity	0	2	Hyperbilirubinaemia CTC4 (2)
Resolve fever in neutropenia	1	2	All resolved following resolution of neutropenia
Non-assessable	1	2	Bone marrow transplant not neutropenic (1); bacterial pneumonia (1), Gram-negative bacteraemia (1)

liposomal amphotericin B for these conditions did respond to treatment ($P=0.14$).

Patients with IPA showed an increase in radiological scores at day 7 compared with the baseline value. However, the increase was more marked in patients treated with caspofungin ($P=0.13$). Radiological improvement was first documented at 14 days of treatment with liposomal amphotericin B, but not until day 21 of caspofungin treatment (Fig. 1).

Toxicity

The proportion of episodes treated with liposomal amphotericin B with at least one defined adverse drug event was higher (83.7%) compared with caspofungin-treated episodes (58.3%) ($P=0.02$). In the liposomal amphotericin B treatment group, 65.3% of episodes were associated with hypokalaemia compared with 33.3% ($P=0.01$) in the caspofungin-treated group, and 36.7% of liposomal amphotericin B-treated episodes had infusion-related rigors compared with 16.7% on caspofungin ($P=0.08$) (Table 4). Two of 24 episodes (8.3%) treated with caspofungin were discontinued as a result of drug toxicity compared with 8/49 (16.3%) on liposomal amphotericin B ($P=0.48$).

Mortality

Eight episodes resulted in death (Table 5). Of these, 6/24 (25.0%) followed caspofungin treatment and 2/49 (4.1%)

followed liposomal amphotericin B treatment ($P=0.013$). The primary cause of death was an IFI in four episodes (16.7%) of caspofungin treatment and one episode (2%) of liposomal amphotericin B treatment ($P=0.037$). Bacterial and other causes accounted for the remaining three patients. The length of treatment was similar in the two treatment groups.

In one patient with *Candida albicans* fungaemia, there was a delay of 4 days in initiating caspofungin treatment, which was given for only 2 days prior to death.

The other candidaemic patient was infected with *Candida tropicalis*. Although treatment with caspofungin was started promptly and the organism was fully sensitive to fluconazole, amphotericin B and itraconazole (MICs of 0.19, 0.25 and 0.012 $\mu\text{g ml}^{-1}$, respectively), and therefore probably to caspofungin (although not tested), and the patient received 6 days of treatment, death occurred from multiorgan failure.

The third IFI death under caspofungin treatment was due to fungal sinusitis, epicenter ethmoid and maxillary sinuses with perosseous intraorbital extension.

The final IFI death under caspofungin treatment had an IPA fungal volume of 59.03 cm^3 , which did not change despite 14 days of caspofungin treatment. The terminal 3 days were further complicated by methicillin-resistant *Staphylococcus aureus* bacteraemia.

Factors associated with mortality on univariate analysis were: severe sepsis/septic shock ($P=0.03$), a shorter duration of antifungal treatment ($P=0.02$), a longer duration of neutropenia of between 100 and 500 ($P=0.008$) and caspofungin drug treatment ($P=0.01$). When these were entered into a multivariate logistic regression model, antifungal treatment with caspofungin remained an independent predictor of mortality [odds ratio = 7.6 (95% confidence intervals 1.2–45.5)].

Salvage therapy

There were 15 episodes of treatment failures that survived and were available for treatment with alternative antifungal drugs (Table 6). Of the four failures on caspofungin, all were

Fig. 1. Radiographical scores for patients with IPA.

Table 4. Toxicity results

Results are given as the number of episodes. Percentage values are shown in parentheses.

Symptom	Caspofungin (n=24)	AmBisome (n=49)	P value
Liver toxicity	5 (20.8)	18 (36.7)	0.17
Elevated creatinine	4 (16.7)	6 (12.4)	0.72
Hypokalaemia	8 (33.3)	32 (65.3)	0.01
Rigors	4 (16.7)	18 (36.7)	0.08
≥1 Adverse event	14 (58.3)	41 (83.7)	0.02

subsequently treated with liposomal amphotericin B (one as combination therapy) and the success rate was 2/4 (50%). Of the 11 assessable failures with liposomal amphotericin B, 9/11 (81.8%) were treated with caspofungin (two as combination therapy) and this resulted in a successful outcome in 4/9 episodes (44.4%). Of the two remaining episodes on liposomal amphotericin B, one was treated with itraconazole and was not assessable, and the other with a high dose (10 mg kg⁻¹ per day) of liposomal amphotericin B with voriconazole and was successful.

Overall assessment of the 97 treatment episodes

When all 97 episodes of treatment with caspofungin or liposomal amphotericin B monotherapy were analysed, the presentations and outcomes were similar to those documented for first-exposure drug therapy. There was an additional death in the caspofungin group when all episodes were considered.

Combination antifungal therapy

Five of the 24 episodes were not considered in the analyses above; these were managed with combination treatment of caspofungin plus liposomal amphotericin B because of the critical clinical condition of the patient (Table 7). Two episodes of *Candida* blood stream infection resulted in death. In one of these, the terminal event was *Stenotrophomonas* septicaemia co-infection. In the other, the dose of

liposomal amphotericin B selected was not increased above 5 mg kg⁻¹ per day. A third episode failed to respond to treatment because of drug toxicity. An episode of *Candida inconspicua* fungaemia did not result in death, despite the development of IPA soon after starting treatment. The recovery was further complicated by hepatosplenic candidiasis, despite combination therapy. This complication was successfully managed with prolonged caspofungin treatment. One episode of IPA was managed successfully.

DISCUSSION

Over the 32-month period of use, twice as many episodes were managed with liposomal amphotericin B as with caspofungin. The lower performance status of patients on admission to hospital indicated that patients treated with caspofungin may have been more sick than liposomal amphotericin B recipients. This suggested that physicians were willing to prescribe the newly available caspofungin, even to sick patients. The larger number of episodes treated with liposomal amphotericin B therefore probably reflects a general hesitancy in using the new antifungal drug, as current experience with liposomal amphotericin B has been favourable.

Episodes of NF and all episodes of IFI were generally treated equally with caspofungin or liposomal amphotericin B, but slightly more episodes of IPA were given liposomal amphotericin B treatment, reflecting the current guidelines

Table 5. Mortality results

Abbreviations: ARDS, acute respiratory distress syndrome; BL, Burkitt's lymphoma.

Disease	Indication for antifungal treatment	Primary cause of death	Disease status at death	Neutrophil status at death ($\times 10^9 \text{ l}^{-1}$)	Antifungal drug	Mean length of treatment (range)
ALL	Neutropenic fever	Haematological disease	Persistence	<0.1	Caspofungin	7.5 days (2–13)
AML	Candidaemia	Candidaemia	Unclear	<0.1	Caspofungin	
AML	Fungal sinusitis	Fungal sinusitis	Persistence	1.0	Caspofungin	
ALL	Candidaemia	Candidaemia	Unclear	<0.1	Caspofungin	
AML	IPA	IPA	Unclear	0.51	Caspofungin	
BL	Neutropenic fever	Haematological disease	Persistence	<0.1	Caspofungin	
AML	Neutropenic fever	ARDS/pneumonia	Unclear	<0.1	AmBisome	9.5 days (5–14)
ALL	Fungal sinusitis	Fungal sinusitis	Persistence	0.36	AmBisome	

Table 6. Secondary (salvage) treatment outcomes for 15 assessable episodes

Indication	Primary drug	Reason for drug change	Secondary treatment	Outcome
NF	Caspofungin	IFI	AmBisome	Death from IPA
IPA + candidaemia	Caspofungin	No response	AmBisome + caspofungin	Failure
NF	Caspofungin	No response	AmBisome	Complete response
NF	Caspofungin	IFI (candidaemia)	AmBisome	Complete response
HSC	AmBisome	Drug toxicity + deterioration	Caspofungin	Partial response
IPA	AmBisome	No response	Caspofungin	Failed
NF	AmBisome	Candidaemia	High-dose AmBisome + voriconazole	Complete response
IPA	AmBisome	No response	AmBisome + caspofungin	Complete response
NF	AmBisome	Drug toxicity	Caspofungin	Complete response
IPA	AmBisome	Deterioration	Caspofungin	Stable disease
NF	AmBisome	Drug toxicity	Caspofungin	Death from haematological disease
NF	AmBisome	No response	Itraconazole	Not assessable
IPA	AmBisome	No response	Caspofungin	Modified complete response
IPA	AmBisome	Drug toxicity	Caspofungin	Failed
IPA	AmBisome	No response	AmBisome + caspofungin	Failed

that caspofungin should be used for salvage treatment of IPA (Maertens *et al.*, 2004). Nevertheless, there are reports of its efficacy when used as the primary therapy for IPA (Candoni *et al.*, 2005). The episodes of invasive candidal infections, extrapulmonary IFI and unspecified or mixed IFI were more often managed with caspofungin.

Response rates in NF were similar for both drug treatments, consistent with the findings of a large prospective comparative clinical trial (Walsh *et al.*, 2004). The improvement in the favourable response rate when allowance was made for defervescence just after recovery from neutropenia (modified response) in caspofungin-treated episodes was interesting. This may suggest a slower antifungal response from caspofungin compared with AmBisome during ongoing neutropenia. The main reason for caspofungin failure was a significantly greater number of breakthrough IFIs ($P=0.047$). These included *Cryptococcus* species, against which caspofungin has no activity. In contrast, the study by Walsh *et al.* (2004) showed no difference in breakthrough IFIs between treatments. One explanation may be the use of azole prophylaxis in 56 % of each treatment group in that study, which could have given a sequential synergistic antifungal advantage (Mukherjee *et al.*, 2005) for the caspofungin group, whereas no patient in our study received antifungal prophylaxis. IFIs other than *Candida* species and *Aspergillus* species are emerging as important causes of NF, many of which are resistant to caspofungin. In order that these fungi are therapeutically covered, the broader spectrum liposomal amphotericin B is preferred.

Favourable responses for IPA episodes were similar in frequency for both antifungal drugs in our study. This is encouraging and suggests that caspofungin can be used effectively as an initial treatment for IPA, as has been described recently (Candoni *et al.*, 2005). All episodes in which at least a modified favourable response was observed

on initial intravenous treatment with caspofungin or liposomal amphotericin B then received oral voriconazole or itraconazole to complete their treatment upon hospital discharge. No patient who was given oral treatment died from IPA within 3 months of hospital discharge. A longer-term follow-up of these patients was not carried out in this study.

Volume changes in IPA episodes assessed by weekly serial CT chest scans indicated a difference in this parameter of response between caspofungin and liposomal amphotericin B treatment. Volumes were similar on day 1 of treatment and both treatment groups showed a volume increase at 7 days, consistent with previous observations (Caillot *et al.*, 2001). However, the increase was greater in caspofungin-treated episodes. Furthermore, radiological improvement was not seen before day 21 in the caspofungin-treated episodes but was apparent by day 14 with liposomal amphotericin B treatment (Fig. 1).

The lower favourable response seen for invasive candidal and other IFIs treated with caspofungin is of concern. No episode of candidaemia or hepatosplenic candidiasis responded to caspofungin, whereas three of the four episodes treated with liposomal amphotericin B responded. Previous studies using caspofungin to treat candidaemia had a low accrual of neutropenic patients (Mora-Duarte *et al.*, 2002) and the outcome in that subgroup may not have been assessed distinctly.

The action of caspofungin may be predominantly fungistatic rather than fungicidal against mould infections, which may be of concern in persistently neutropenic patients (Denning, 2003). In contrast, amphotericin B is fungicidal. It has been demonstrated that viable *Aspergillus* hyphae persist *in vitro* (Bowman *et al.*, 2002), and in animal models fungal clearance is incomplete with caspofungin compared with amphotericin B (Denning, 2003). Our findings of

Table 7. Results of combination therapy

Abbreviations: M, male; F, female; ind, induction chemotherapy; HSC, hepatosplenic candidiasis; K⁺, potassium toxicity; Cr, elevated creatinine; Bi, elevated bilirubin; Ri, rigors; CTC, clinical toxicity criteria grade; MOF, multiorgan failure; Steno, *Stenotrophomonas* spp. bacteraemia.

Sex/age	Disease	Neutropenic status ($\times 10^9 \text{ l}^{-1}$)	IFI	Indication	Liposomal amphotericin B dose	Duration of treatment	Follow-up treatment	Toxicity	Outcome	Notes
M/32 years	ALL ind	0.2 $\times$ 8 days	<i>C. inconspicua</i>	Severe sepsis	3 mg $\times$ 12 days; 5 mg $\times$ 11 days	23 days	Itraconazole $\times$ 14 days	Nil	Partial success	Developed IPA on treatment; developed HSC 30 days later
F/15 years	ALL ind	0.1 $\times$ 5 days	IPA	Severe sepsis	3 mg	11 days	Nil	K ⁺ CTC3	Partial success	Modified complete response
M/47 years	AML ind	0.1	<i>C. albicans</i>	Septic shock	5 mg	6 days	Nil	K ⁺ CTC1	Died from IFI	MOF, skin dissemination
M/40 years	ALL ind	0.8 $\times$ 2 days	HSC	Severe sepsis	5 mg	17 days	Caspofungin	K ⁺ CTC3, Cr CTC3, Bi CTC3	Failed	Discontinued treatment for toxicity + disease progression
F/34 years	ALL ind	0.1	<i>C. tropicalis</i>	Septic shock	5.5 mg $\times$ 7 days; 10 mg $\times$ 5 days	15 days	Nil	Ri CTC2	Died from IFI + bacteraemia + MOF	Terminal Steno

the slower radiological resolution, and the more frequent poorer responses with caspofungin in candidal and other IFIs that were documented, suggest that there may be clinically relevant translations of the *in vitro* and animal data. This may be clinically significant in patients at risk of rapid clinical deterioration, which is frequently observed in candidal infections, for example (Ellis *et al.*, 2003). Patients with IPA, on the other hand, generally have a more stable course. The sequential use of voriconazole (a fungicidal drug) may be a factor resulting in the similar modified response rates and survival seen in our patients treated with either caspofungin or liposomal amphotericin B.

More of the episodes treated with caspofungin compared with liposomal amphotericin B resulted in fungus-related deaths. Two of these were associated with candidaemia. A delay in treatment may well have been a factor contributing to one death. The other candidaemic patient was infected with *C. tropicalis*. Literature evidence of the efficacy of caspofungin in candidaemia has not included large studies within neutropenic subgroups, particularly in critically septic patients (Hughes *et al.*, 2002; Pappas *et al.*, 2004). Response rates in neutropenic patients, however, are generally low (Denning, 2003). Although the fungus associated with sinusitis in the third death episode was not identified, the possibility of *Mucorales* should be considered and high-dose liposomal amphotericin B or posaconazole given rather than caspofungin, as these fungi are resistant to candins. This observation illustrates the need to use a broader-spectrum agent than caspofungin where there is a possibility of a non-*Aspergillus* mould infection. The fourth episode of IFI death had a substantial lung fungal burden, which proved impossible to clear. The suboptimal antifungal and static > cidal activity among the candins, resulting in failure to clear galactomannaemia or reduce tissue burden (Denning, 2003), is therefore relevant to this particular observation.

The severity of sepsis, the length of antifungal treatment and protracted neutropenia were additional factors in caspofungin treatment that were significantly associated with patient death. However, multiple logistic analysis confirmed that caspofungin therapy itself was an independent predictor of mortality, the excess mortality in this group of patients mainly being due to IFIs. In such a small sample size in a non-blind, non-randomized study of retrospective design, there is a strong possibility of prescribing and other biases, for example from analysing episodes, that may confound our treatment-related observations. Furthermore, inclusion of some cases of a diagnostic category that were not definite or probable IFIs could have influenced the outcome. However, such strict criteria, which are normally required in prospective clinical studies, often do not reflect the clinical reality and patient diversity present in a clinical setting. Therefore, the fact remains that our results reflect the current patterns for the use of and the outcome from using two antifungal drugs in a genuine clinical setting, with the objective end point of death as the primary response determinant. Therefore, our clinical experience is consistent

with the lack of activity of caspofungin against certain fungi, the mooted concern over its use in neutropenic candidaemic patients and the persistence of viable fungal elements that have been found *in vitro* and in animal models.

Despite accumulating evidence that a combination of caspofungin and amphotericin B reduces MICs and tissue fungal burden and enhances survival in animal models, there is little or no evidence of such an effect from human studies (Kontoyiannis & Lewis, 2004). Our findings also do not suggest that there is an enhanced clinical benefit from combination therapy in patients with enhanced sepsis due to candidosis or IPA, with only one of the five patients (the patient with IPA) having a response and/or surviving for longer than 1 month.

In conclusion, broadly similar responses for caspofungin and liposomal amphotericin B were seen when treating IFIs or NF. However, the higher level of overall as well as fungal-related mortalities, the delays in clinical and radiological response and the increased number of breakthrough IFIs occurring with caspofungin suggest that there may be an antifungal-drug-dependent clinical difference in outcome. This observation requires further study.

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REFERENCES

- Ascioglu, S., Rex, J. H., de Pauw, B. & 17 other authors (2002). Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* **34**, 7–14.
- Bowman, J. C., Hicks, P. S., Kurtz, M. B., Rosen, H., Schmatz, D. M., Liberator, P. A. & Douglas, C. M. (2002). The antifungal echinocandin caspofungin acetate kills growing cells of *Aspergillus fumigatus* *in vitro*. *Antimicrob Agents Chemother* **46**, 3001–3012.
- Caillot, D., Casanovas, O., Berbard, A. & 10 other authors (1997). Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* **15**, 139–147.
- Caillot, D., Couaillier, J.-F., Bernard, A. & 8 other authors (2001). Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol* **19**, 253–259.
- Candoni, A., Mestroni, R., Damiani, D., Tiribelli, M., Michelutti, A., Silvestri, F., Castelli, M., Viale, P. & Fanin, R. (2005). Caspofungin as first line therapy of pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. *Eur J Haematol* **75**, 227–233.
- Coiffier, B., Lepage, E., Brière, J. & 10 other authors (2002). CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* **346**, 235–242.
- Denning, D. (2003). Echinocandin antifungal drugs. *Lancet* **362**, 1142–1151.
- Ellis, M., Hedstrom, U., Jumaa, P. & Bener, A. (2003). Epidemiology, presentation, management and outcome of candidemia in a tertiary care teaching hospital in the United Arab Emirates, 1995–2001. *Med Mycol* **41**, 521–528.
- EORTC, International Antimicrobial Therapy Cooperative Group (1989). Empirical antifungal therapy in febrile granulocytopenic patients. *Am J Med* **86**, 668–672.
- Farag, S. S., Ruppert, A. S., Mrózek, K. & 15 other authors (2005). Outcome of induction and postremission therapy in younger adults with acute myeloid leukemia with normal karyotype: a cancer and leukemia group B study. *J Clin Oncol* **23**, 482–493.
- Hughes, W. T., Armstrong, D., Bodey, G. P. & 8 other authors (2002). 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* **34**, 730–751.
- Kami, M., Kishi, Y., Hamaki, T. & 11 other authors (2002). The value of the chest computed tomography halo sign in the diagnosis of invasive pulmonary aspergillosis. An autopsy-based retrospective study of 48 patients. *Mycoses* **45**, 287–294.
- Karthaus, M. & Cornely, O. (2005). Recent developments in the management of invasive fungal infections in patients with hematological malignancies. *Ann Hematol* **84**, 207–216.
- Kontoyiannis, D. P. & Lewis, R. E. (2004). Toward more effective antifungal therapy: the prospects of combination therapy. *Br J Haematol* **126**, 165–175.
- Lin, S.-J., Schranz, J. & Teutsch, S. (2001). Aspergillosis case-fatality rate: systematic review of the literature. *Clin Inf Dis* **32**, 358–366.
- Maertens, J., Raad, I., Petrikos, G. & 10 other authors (2004). Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Inf Dis* **39**, 1563–1571.
- Medical Research Council Working Party on Leukemia in Adults (2006). Medical Research Council Acute Lymphoblastic Leukemia Trial XII (ULALL XII), Version 4.1, February 2006. Joint Trial with Eastern Cooperative Oncology Group (ECOG) – E2993. Protocol for Adults with ALL. Modified for Intrathecal Therapy and Philadelphia Positive ALL, July 2002. Revised May 2005, February 2006. Available at <http://www.ctsu.ox.ac.uk/projects/ukallxii/>
- Mora-Duarte, J., Betts, R., Rotstein, C. & 7 other authors (2002). Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* **347**, 2020–2029.
- Mukherjee, P. K., Sheehan, D. J., Hitchcock, C. A. & Ghannoum, M. A. (2005). Combination treatment of invasive fungal infections. *Clin Microbiol Rev* **18**, 163–194.
- Ostrosky-Zeichner, L., Marr, K., Rex, J. & Cohen, S. (2003). Amphotericin B: time for a new “gold standard”. *Clin Inf Dis* **37**, 415–425.
- Pappas, P. G., Rex, J. H., Sobel, J. D., Filler, S. G., Dismukes, W. E., Walsh, T. J. & Edwards, J. E. (2004). Guidelines for treatment of candidiasis. *Clin Inf Dis* **38**, 161–189.
- Walsh, T. J., Teppler, H., Donowitz, G. R. & 8 other authors (2004). Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* **351**, 1391–1402.