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An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients

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***Objectives*: Caspofungin was evaluated as first-line monotherapy of invasive aspergillosis (IA) in patients with haematological malignancies and undergoing autologous transplants.**

***Methods*: Adults with proven or probable IA, defined strictly according to EORTC-MSG criteria, were eligible. Those with possible IA were enrolled, but were not evaluable for efficacy unless upgraded to proven/probable disease within 7 days of registration based on investigations performed within 48 h after enrolment. Caspofungin dosage was 70 mg (day 1) followed by 50 mg/day. The primary endpoint was the proportion of patients with complete or partial response at the end of caspofungin therapy in the modified intention to treat (MITT) group; secondary endpoints were response and survival at day 84 and safety.**

***Results*: In the MITT group ($n = 61$), 75% of patients had cancer not in remission (relapsing or refractory), 85% were neutropenic at enrolment and 49% had a Karnofsky score of $\leq$50. At end of treatment, 1 and 19 patients had complete and partial response, respectively [success rate 33% (20/61)], 9 (15%) achieved stabilization and 31 (51%) had disease progression. One patient was not evaluable. The 6 and 12 week survival rates were 66% (40/61) and 53% (32/60), respectively. Baseline characteristics associated with survival at day 84 were an underlying disease in remission (not relapsing or refractory) and Karnofsky score. Recovery from neutropenia at the end of treatment was also significantly associated with survival. No serious drug-related adverse events or discontinuations due to drug-related adverse events were observed.**

***Conclusions*: Caspofungin provided an observed response rate compatible with the null hypothesis of a true response rate of $\leq$35%. Underlying disease-related factors had a major impact on results.**

Keywords: acute leukaemia, fungal infections, echinocandins

Introduction

Invasive aspergillosis (IA) develops in 5%–10% of patients treated for acute leukaemia and in up to 40% of recipients of allogeneic haematopoietic stem cell transplants (HSCTs).[1–3] Although recent data suggest improved survival,[2] in general IA-associated mortality ranges between 50% and 80% in patients with leukaemia and up to 70% in HSCT recipients.[1–7] Confirming a diagnosis of IA before death remains problematic, particularly because of the difficulty in obtaining cultures and

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biopsies from sterile sites. As a consequence the European Organization for Research and Treatment of Cancer Infectious Disease Group and the Mycoses Study Group (EORTC-MSG) proposed consensus definitions for different levels of diagnostic certainty.[8] These criteria, recently updated,[9] take into account patient risk of developing IA, suggestive clinical presentation, laboratory data and imaging tests. According to the old criteria, the diagnosis of probable IA requires microbiological data supporting the likelihood of disease, including a positive culture and microscopy from a non-sterile site. The new definitions have added a positive galactomannan (GM) and/or glucan test as able to support a diagnosis of probability. The two largest randomized clinical trials of IA to date included many patients based on suggestive radiological imaging, without any microbiological confirmation.[10,11]

Caspofungin has proved effective for salvage therapy of IA and it has been approved for this indication. Caspofungin is very well tolerated, even in patients with severe underlying conditions.[12] However, there were very little published data about the efficacy of caspofungin as first-line therapy. For this reason, we found it important to perform a clinical trial aimed at estimating the efficacy of caspofungin as first-line monotherapy of patients with proven or probable IA, as defined by strict EORTC-MSG criteria. Patients with haematological malignancies and autologous HSCT (Group 1) and patients with allogeneic HSCT (Group 2) were included in two different strata and evaluated separately, because response rates (RRs) and survival differ substantially in these populations. In the present article we report results among patients with haematological malignancies or undergoing autologous HSCT. Results from patients with allogeneic HSCT will be reported separately due to the very different nature of the patient populations and underlying diseases. Data about haematological patients were presented at the TIMM (Trends in Medical Mycology) Congress in Torino 2007 as an oral presentation by C. V.

Methods

This was a Phase II, open label, non-comparative, multicentre study to estimate the efficacy of caspofungin as first-line monotherapy for IA in patients with haematological malignancies or undergoing autologous HSCT. Twenty centres in Europe participated in the study, which was approved by the Protocol Review Committee of the EORTC (EORTC and EudraCT protocol numbers 65041 and 2004-002944-90, respectively) and by the Ethics Committees of each participating institution. Written informed consent was required and enrolment was centralized at the EORTC Data Centre using a secure web-based system. All case reports were computerized at the EORTC Data Centre in Brussels, Belgium and reviewed by a Data Review Committee (DRC) for completeness, accuracy, eligibility criteria and assessment of the outcome variables. The study was funded by an unrestricted educational grant by Merck & Co. One representative from Merck participated in DRC meetings, with no voting rights. Patients received a 70 mg loading dose of caspofungin on day 1, followed by 50 mg/day for at least 15 days (or until failure) and up to 84 days. Dose modifications were made for patients with body weight >80 kg (70 mg/day), moderate hepatic failure (70 mg loading dose followed by 35 mg/day) and concomitant administration of liver inducers able to influence caspofungin concentrations. Addition or modification to protocol therapy in the absence of efficacy assessment was considered treatment failure. Evaluations included medical history, physical examination, Karnofsky score, haematology and chemistry profiles at baseline, weekly and up to 30 days after treatment. In addition, *Aspergillus* GM-ELISA test, blood cultures, sputum cultures, bronchoalveolar lavage (BAL), aspiration of pulmonary and extrapulmonary lesions, CSF examination, chest X-rays, sinus or lung CT scans were performed as clinically appropriate. GM tests were performed at least every 48 h, if possible, especially during the upgrading phase. For the purpose of this trial a GM test of $\geq$0.7 was considered positive, a value that was the most widely used when the study was conceived. Two positive, consecutive samples in blood or one positive sample in BAL were needed in order to contribute to a diagnosis of probable infection.

Study design and entry criteria

The study design is shown in Figure 1. The study included patients with haematological malignancies in any stage, including patients with an underlying disease not in remission (relapsing or refractory) and with probable or proven IA, strictly according to the EORTC-MSG definitions, with the only exception being that the GM test was allowed as a confirmation test for probable aspergillosis. Patients with possible IA (i.e. those with a halo sign only, without microbiological confirmation or with host factors and clinical signs or symptoms compatible with IA but again without microbiological confirmation) were allowed to start treatment. However, investigators had 7 days to upgrade the case to proven or probable IA based on culture or serological tests performed prior to or within 48 h after registration, but with results pending. Patients not upgraded were discontinued from the study; these patients were assessed for safety but not for efficacy. Other entry criteria included age $\geq$18 years and not having received either an investigational agent within 14 days prior to registration or an empirical antifungal therapy (not including an echinocandin) for >72 h before inclusion. Oral prophylaxis had to be discontinued at study entry. No intravenous prophylaxis was allowed, unless with fluconazole. A history of allergy to echinocandins, severe renal failure, significant liver function test abnormalities, severe hepatic insufficiency, inadequately treated bacterial infection, documented HIV infection, status of pregnancy or lactation, conditions hampering compliance and a Karnofsky score of $\leq$20 were exclusion criteria.

Response assessment criteria

The study was evaluated using standard response assessment criteria.[9] Briefly, every case was assessed by clinical and radiological criteria as having achieved complete or partial response (success), stabilization or disease progression (failure). The reduction in the sum of the area and longest diameter of all measurable lesions attributable to IA from baseline to end of therapy (EOT) was calculated as follows: [sum of the area (or longest diameter) at baseline – sum of the area (or longest diameter) at EOT]/sum of the area (or longest diameter) at baseline.

A negative reduction indicated an increase in the lesion area or longest diameter. At least a 50% reduction in the size of the lesion was required to qualify the case as partial response, while a reduction of <50% qualified the patient as having stable disease. The modified intention to treat (MITT) group included all patients with confirmed probable/proven IA who received at least one dose of caspofungin treatment.

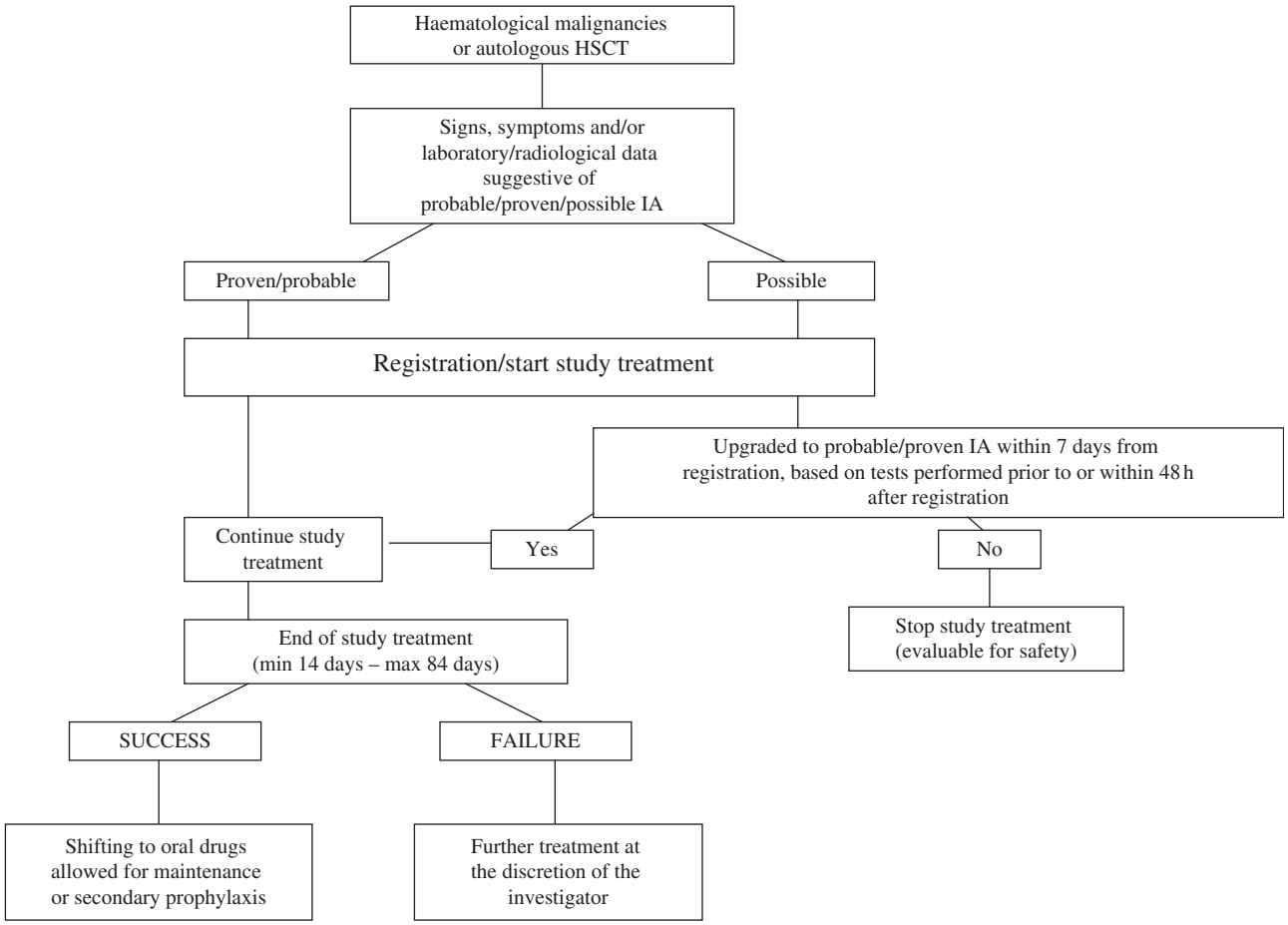

Figure 1. Study design.

Study endpoints and statistical planning

The primary endpoint was the proportion of MITT patients with complete or partial response to treatment at EOT. The secondary endpoints were response to treatment and survival at day 84 after enrolment, and safety, as defined by the proportion of drug-related adverse events, serious drug-related adverse events and drug-related adverse events leading to treatment discontinuation. The study was planned according to a one-stage Fleming design. Based on RRs observed in a previous study,[9] 52 eligible and evaluable patients were needed, in order to show that the true RR was >35% (with a power of 95% in the case of a true RR of 55%), using a one-sided significance level of 10%. To reject the null hypothesis of a true RR of ≤35% (and therefore to recommend the tested regimen for further studies), ≥23 complete or partial responses out of 52 eligible patients were required (observed RR 44%). A non-eligibility rate of 10% and a non-upgrading rate of 30% were forecast; thus, the final sample size estimation was planned to include at least 87 patients. Fisher's exact test was used to test the statistical significance of differences in discrete data and the Mann–Whitney *U*-test to compare continuous variables such as Karnofsky score. $P<0.05$ was considered statistically significant. As most of the deaths attributable to IA occur by day 84, the binary survival status at day 84 was considered as an endpoint. A logistic regression model was constructed to determine baseline characteristics independently related to survival at day 84. The model took into account the granulocyte count at EOT, as well, with the consequence that the resulting logistic regression model cannot be used to predict survival status at start of treatment. Gender, Karnofsky score, status of underlying disease, diagnosis of IA, site of infection, prior antifungal therapy, being neutropenic at enrolment and EOT, and having been neutropenic for >10 days during the 60 days prior to enrolment were variables included in the analysis. The logistic regression model was obtained using stepwise forward selection of variables.

Results

In total, 129 patients were enrolled between 26 April 2005 and 31 March 2007. Sixty-eight patients were ineligible due to lack of microbiological criteria ($n=64$) or absence of major or minor clinical criteria ($n=4$). The remaining 61 cases were evaluable for the MITT analysis, resulting in a statistical power of 0.97. In this study, 88 patients were initially registered as having possible aspergillosis. Of these, 24 (27%) were upgraded to proven or probable IA.

Baseline characteristics and demographics

As shown in Table 1, all patients had a haematological malignancy treated with chemotherapy or autologous HSCT and were affected by proven or probable IA. Neutropenia (<500 cells/mm^3) at enrolment and/or for >10 days within the 60 days before was present in more than two-thirds of the patients. At EOT, the rate

Table 1. Baseline patient characteristics in the MITT group

Characteristic	MITT ($N=61$)
Age in years, median (range)	64 (19–86)
Gender, *n* (%)	
male	43 (70)
Prior antifungal therapy, *n* (%)	
none	12 (20)
empirical	8 (13)
prophylactic	33 (54)
empirical and prophylactic	8 (13)
Underlying disease not in remission (relapsing or refractory), *n* (%) (not assessable for two patients)	44 (75)
Underlying conditions, *n* (%)	
ALL	4 (7)
AML	34 (56)
chronic leukaemia	9 (15)
lymphoma (NHL/HD)	11 (18)
other (MDS, multiple myeloma)	3 (5)
Diagnosis of IA, *n* (%)	
proven	1 (2)
probable	60 (98)
Site of infection, *n* (%)	
lower respiratory tract	60 (98)
sino-nasal infection	1 (2)
Neutropenia (<500 cells/mm^3) at start of study treatment, *n* (%) (not assessable in one case)	51 (85)
Neutropenia (<500 cells/mm^3) for >10 days in the previous 60 days, *n* (%)	44 (72)
Criteria supporting the diagnosis of probable IA, *n*[a]	
positive GM antigen	44
positive culture for *Aspergillus*	8
positive GM antigen and culture	5
positive GM antigen, culture and cytological examination	1
positive cytological examination	1
positive cytological examination and culture	1

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; NHL/HD, non-Hodgkin's lymphoma/Hodgkin's disease; MDS, myelodysplastic syndrome.
[a]Out of 60 patients with probable IA.

of neutropenia was 33% (19/58) (data not shown in the table; missing for three patients). The majority of the patients had a haematological underlying disease that was not in remission (relapsing or refractory) and the median Karnofsky score at enrolment was 60, with 49% (30/61) of the patients with a score of $\leq$50. About two-thirds of the patients (41 of 61; 67%) had received antifungal prophylaxis until enrolment. Regimens used included oral or intravenous fluconazole in 33 cases, oral itraconazole in 5 cases and another oral combination in the other cases. Empirical antifungal therapy was administered in 16 of 61 (26%) patients, of whom 8 had also received antifungal prophylaxis. Regimens used for empirical therapy included amphotericin B (usually the standard formulation) in nine cases and voriconazole in seven cases. Empirical antifungal therapy was administered for 1, 2 and 3 days in three, three and nine patients, respectively. One patient received empirical deoxycholate amphotericin B for 7 days and was kept in the study because this was considered as a minor violation by the DRC. Criteria supporting a diagnosis of probable IA were mainly a positive GM test, with or without positive culture or cytological examination. The median GM value in patients with positive test results was 1.45 (0.7–6.33) in blood and 3.57 (0.7–23.5) in BAL. A total of 16 of 61 patients had positive cultures for *Aspergillus*. Pathogens isolated were *Aspergillus fumigatus* ($n=15$), *Aspergillus flavus* ($n=2$) and *Aspergillus niger* ($n=1$). Two patients had two different species isolated. The most common clinical signs and symptoms were sputum production (92%), fever (77%), cough (67%), dyspnoea (51%) and chest pain (38%).

Outcomes

The mean duration of treatment was 27 days (SD $\pm$24), with a median duration of 15 days (range 3–84). RRs at EOT are shown in Table 2. Among the nine patients with stable disease at EOT, six survived day 84. Of them, two did not receive any additional antifungal treatment after $\sim$3 weeks of caspofungin

Table 2. Response to treatment at EOT in the MITT population

Response	MITT population ($N=61$)	
	n	% (95% CI)
Complete	1	2 (0–9)
Partial	19	31 (20–44)
Stable disease	9	15 (7–26)
Disease progression	31	51 (38–64)
Not evaluable[a]	1	2 (0–9)

[a]Patient refused treatment.

and four received maintenance therapy with an oral azole (two itraconazole and two voriconazole). Response to treatment by baseline patient characteristics is shown in Table 3. The Karnofsky score at the start of treatment had a statistically significant impact on the outcome (Mann–Whitney *U*-test; $P=0.04$). Although not statistically significant, more treatment failures were observed among patients with acute versus chronic leukaemia, with neutropenia at the start of study treatment and, especially, among those with a history of severe and prolonged neutropenia in the 60 days prior to enrolment ($P=0.07$). Survival data at day 84 are reported for 60 patients, with 1 patient lost to follow-up. The survival rates at 6 and 12 weeks were 66% (40/61) and 53% (32/60), respectively. The most

Table 3. Response to treatment at EOT by baseline characteristics

	Success, *n*/*N* (%)	*P* value
Gender		
male	15/43 (35)	0.77
female	5/18 (28)	
Underlying condition		
acute leukaemia	10/38 (26)	0.22
chronic leukaemia	5/9 (56)	
other	5/14 (36)	
Status of underlying disease (not assessable for two patients)		
not in remission (relapsing or refractory)	15/44 (34)	0.75
in remission	4/15 (27)	
Diagnosis of aspergillosis		
proven at start of treatment	0/1 (0)	1
probable at start of treatment	12/36 (33)	
possible at start of treatment, upgraded to probable	8/24 (33)	
GM value (GM was not evaluated in one patient)[a]		
not positive	3/9 (33)	1
positive	17/51 (33)	
Prior antifungal therapy		
no	6/12 (50)	0.26
empirical (only or in combination with prophylaxis)	5/16 (31)	
prophylaxis	9/33 (27)	
Previous bacterial infection		
no	15/47 (32)	1
yes	5/14 (36)	
Site of infection		
lower respiratory tract	19/60 (32)	0.33
sino-nasal	1/1 (100)	
Neutropenia for >10 days in the previous 60 days		
no	9/17 (53)	0.07
yes	11/44 (25)	
Neutropenia at enrolment (not assessable in one case)		
no	5/9 (56)	0.14
yes	15/51 (29)	
Karnofsky score		
<50	2/14 (14)	0.04
50–60	7/21 (33)	
>60	11/26 (42)	

[a]GM was positive in the proven IA case.

common 12 week cause of death was IA, alone ($n=18$) or in association with other causes, such as haemorrhage (two cases), the underlying malignancy (five cases), a non-fungal concomitant infection (one case) and other causes (two cases). Variables significantly associated with survival at day 84 in the multivariate analysis were having an underlying disease in remission (not relapsing or refractory) at baseline (remission versus not in remission: OR 37.52; 95% CI 2.64 to >999), Karnofsky score at start of treatment (for each increase in the score the odds of survival increased by 88%, i.e. OR 1.88; 95% CI 1.12–3.58) and presence of neutropenia at EOT (presence versus absence: OR 0.04; 95% CI <0.001–0.38). RRs of 16% (3/19) and 41% (16/39) were observed among patients who were and were not neutropenic at EOT, respectively ($P=0.08$). Neutropenia at EOT was not assessable in three patients. Among the nine patients who were not neutropenic at the start of therapy, one was lost to follow-up. Five of the other eight (63%) survived to day 84. Antifungal prophylaxis and/or empirical therapy had no influence on response to treatment and survival, nor did the dose per weight of caspofungin administered.

Radiological assessments

Radiological assessments were available in 49 of 61 (80%) patients. Of the 12 patients with no radiological assessments at EOT, 11 had a clinical assessment of disease progression and one voluntarily refused treatment and was not assessed. In four patients, the radiological assessment was based on chest X-ray data only. Therefore, exact calculations of the change in size of the lesion were performed in 45 patients. Partial response was associated with a 73% (53%–90%) median decrease in the sum of the areas of all measurable lesions attributable to IA. A median 36% reduction was noted for patients with stable disease. Conversely, patients with disease progression differed significantly, with a median increase in the lesion size of 103% (95% CI 69–421). No differences were demonstrated in terms of defervescence, sputum production, cough, dyspnoea and chest pain between responding and stabilized patients.

Safety

Of the 129 patients included in the safety analysis, 15% ($n=19$) had drug-related adverse events. There were no serious drug-related adverse events or drug-related adverse events leading to caspofungin discontinuation. Grade III or IV adverse events categorized as 'likely related' by the local investigator were all laboratory abnormalities in γ-glutamyl transferase ($n=5$), alkaline phosphatase ($n=4$), bilirubin ($n=2$), aspartate aminotransferase ($n=1$) and kalaemia ($n=3$). No grade V adverse events were noted as 'likely related' by the local investigator.

Discussion

In our study 33% (95% CI 21–46) of patients in the MITT analysis had a favourable response (complete and partial) at the end of caspofungin therapy. The role of the severity of the underlying disease was quite evident in this study. First, patients with acute leukaemia, Karnofsky score <50 and neutropenia at the start of study treatment appeared less likely to have a favourable response. Secondly, the status of the underlying disease at baseline, the Karnofsky score and being neutropenic at EOT were all significantly associated with survival at day 84. These results suggest that in patients with persistent neutropenia and an underlying disease not in remission (relapsing or refractory), treatment of proven/probable IA presents a unique challenge. Response to treatment and survival were actually lower among patients with 'uncontrolled cancer (active malignancy)' than in other patients in the Ambiload study, as well.[11] The status of the underlying disease was also found to be one of the factors significantly associated with survival in a recent French study.[13]

In terms of diagnostic certainty, this is the first trial to apply the EORTC-MSG criteria strictly.[8] We enrolled only patients with microbiological data supporting a diagnosis of proven/probable aspergillosis and excluded cases of possible disease (i.e. patients with halo sign only). This is important because better outcomes have been observed in patients enrolled solely on the basis of radiological signs than in patients with proven or probable disease.[14] Indeed, patients enrolled based on the presence of the halo sign only had better RRs than other patients in both the Phase II and III voriconazole studies and in the Ambiload study,[10,11,15] suggesting that at least some of the patients with radiological signs only actually do not have IA. It is important to note that requiring some microbiological confirmation of IA does not mean treating patients at a more advanced stage of disease, since treatment was always started at first clinical signs and empirical therapy was allowed, although for no longer than 72 h. Multivariable analyses showed that previous antifungal therapy or prophylaxis had no impact on response to treatment and survival.

Debate exists as to whether or not patients with stable disease should be considered as success of therapy. In our study, the main difference between stable disease and partial response was in the extent of decrease in the size of the lesions, with no difference in clinical outcomes, including GM values. As suggested in a recent position paper, given the severity of both the underlying condition and the complicating infection, there may be cases in which both physicians and patients might consider stable disease as an acceptable outcome.[16]

This study was a non-comparative Phase II study designed to explore the efficacy of caspofungin as first-line therapy of IA. When the present study was designed, the only available model for setting reference RRs and calculating the sample size was the voriconazole versus amphotericin B study.[10] However, this choice, although forced, might have been inappropriate, because of the existence of important methodological differences between this study and the one we were planning. Indeed, the voriconazole study evaluated response to treatment at day 84, regardless of any therapeutic modification, and not at EOT, as in our study; it included both patients with haematological malignancies and allogeneic transplants and allowed the inclusion of patients lacking any microbiological or serological documentation of IA.

In conclusion, caspofungin achieved an EOT RR of 33% in the MITT population and a day 84 survival rate of 53%. We found that an underlying disease not in remission (relapsing or refractory), a Karnofsky score of <50 and persistent neutropenia were all negatively associated with survival. While the planned null hypothesis of a true RR of ≤35% could not be rejected, it is possible that this was related to the very high-risk patient population included and to the choice of enrolling

only patients with a high degree of disease certainty (proven/probable IA). Comparisons between trials are often impossible, because of the differences in definitions and patient populations and should, therefore, be interpreted with great caution. In this study, RRs at EOT and survival appeared to be slightly lower than those obtained with voriconazole and liposomal amphotericin B in patients with a similar disease certainty (with much better safety), but comparable to those obtained with the same drugs in patients with a similar underlying disease status. We do not know what the RR was in the voriconazole and liposomal amphotericin B trials among patients who had at the same time a true proven/probable disease and an advanced haematological neoplasm.

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Transparency declarations

C. V. has been a consultant to Astellas, Gilead, MSD, Pfizer and Schering-Plough, has been a member of speakers' bureaus for Gilead, Pfizer and Schering-Plough, and has received research grants from Pfizer, Merck, Gilead, BMS and Abbott. R. H. has been a consultant to Astellas, Gilead, MSD, Pfizer and Schering-Plough, has been a member of speakers' bureaus for Gilead, Pfizer and Schering-Plough, and has received research grants from Pfizer. O. M. has received research grants from Bio-Rad, Essex/Schering-Plough, Merck, Pfizer, Roche Diagnostics and Wako, and has been a consultant for and has been a speaker at conferences organized by Essex/Schering-Plough, Merck and Pfizer. M. S. is an employee of Merck & Co., Inc., USA and owns stock and/or stock options in the company. A. U. has been a consultant to Astellas, Basilea, Gilead, MSD, Schering-Plough and Pfizer, and has been a member of speakers' bureaus for Astellas, Gilead, MSD, Schering-Plough and Pfizer. R. M. has been a speaker for Merck/MSD and Zeneus/Cephalon. J. M. has received research grants from Merck/MSD and Pfizer, is a consultant to Astellas, Bio-Rad, Merck/MSD, Nektar, Pfizer, Schering-Plough, F2G, Zeneus/Cephalon and Luminex, and has served on the speakers' bureaus of Astellas, Bio-Rad, Merck/MSD, Pfizer, Schering-Plough, Zeneus/Cephalon and Viropharma. All other authors: none to declare.

The study design was discussed with Merck representatives and finally approved by the EORTC Protocol Review Committee. A Merck representative was present at every meeting of the DRC without voting rights. Results were discussed with Merck representatives, who played no role in the study analysis.

Writing assistance was provided by Wendy Horn PhD.

Author contributions

C. V. designed the study and wrote the study protocol and the final article. R. H., H. A., O. M. and A. J. U. included patients and were members of the DRC. L. B. is the EORTC Clinical Research Physician responsible for the EORTC Infectious Disease Group and was part of the DRC. A. S., A. Gallamini and A. Giagounidis were the main contributors in terms of patients. L. M. is the EORTC Infectious Disease Group Data Manager. R. M. provided cases and was the trial co-coordinator. M. P. and L. A. are the Group Statisticians. M. S. is the Merck representative, who participated in the DRC meetings with no voting rights. J. M. included cases and was the EORTC Infectious Disease Chairman at the time the study was conducted.

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