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Safety and Efficacy of Itraconazole Compared to Amphotericin B as Empirical Antifungal Therapy for Neutropenic Fever in Patients with Haematological Malignancy*

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Key Words
Amphotericin B · Antifungal therapy, empirical · Itraconazole · Neutropenia · Fever, unresolved

Summary
Background: Safety, tolerability and efficacy of itraconazole and amphotericin B (AMB) were compared for empirical antifungal treatment of febrile neutropenic cancer patients. **Patients and Methods:** In an open, randomised study, 162 patients with at least 72 h of antimicrobial treatment received either intravenous followed by oral itraconazole suspension or intravenous AMB for a maximum of 28 days. Permanent discontinuation of study medication due to any adverse event was the primary safety parameter. Efficacy parameters included response and success rate for both treatment groups. **Results:** Significantly fewer itraconazole patients discontinued treatment due to any adverse event (22.2 vs. 56.8% AMB; $p < 0.0001$). The main reason for discontinuation was a rise in serum creatinine (1.2% itraconazole vs. 23.5% AMB). Renal toxicity was significantly higher and more drug-related adverse events occurred in the AMB group. Intention-to-treat (ITT) analysis showed favourable efficacy for itraconazole: response and success rate were both significantly higher than for AMB (61.7 vs. 42% and 70.4 vs. 49.3%, both $p < 0.0001$). Treatment failure was markedly reduced in itraconazole patients (25.9 vs. 43.2%), largely due to the better tolerability. **Conclusions:** Itraconazole was tolerated significantly better than conventional AMB and also showed advantages regarding efficacy. This study confirms the role of itraconazole as a useful and safe agent in empirical antifungal therapy of febrile neutropenic cancer patients.

Schlüsselwörter
Amphotericin B · Antimykotische Therapie, empirische · Itraconazol · Neutropenie · Fieber, ungeklärtes

Zusammenfassung
Hintergrund: Es wurden die Sicherheit, Verträglichkeit und Wirksamkeit von Itraconazol und Amphotericin B (AMB) in der antimykotischen Therapie der persistierend febrilen Neutropenie verglichen. **Patienten und Methoden:** In einer offenen, randomisierten Studie erhielten 162 Patienten mit mindestens 72-stündiger antibiotischer Therapie entweder Itraconazol (erst intravenös, dann oral) oder AMB (intravenös) für maximal 28 Tage. Primärer Sicherheitsparameter war die dauerhafte Unterbrechung der Studienmedikation aufgrund von Nebenwirkungen. Die Wirksamkeitsparameter umfassten die Ansprech- und Erfolgsrate für beide Behandlungsgruppen. **Ergebnisse:** Signifikant weniger Itraconazol-Patienten brachen die Behandlung wegen Nebenwirkungen ab (22,2 vs. 56,8% AMB; $p < 0,0001$). Hauptursache für Studienabbrüche war der Anstieg des Serum-Kreatinin-Spiegels (1,2% Itraconazol vs. 23,5% AMB). Nephrotoxische und weitere Nebenwirkungen traten im AMB-Studienarm signifikant häufiger auf. Intention-to-Treat (ITT)-Analysen zeigten eine bessere Wirksamkeit von Itraconazol: Ansprech- und Erfolgsrate waren signifikant höher als unter AMB (61,7 vs. 42% und 70,4 vs. 49,3%, beide $p < 0,0001$). Behandlungsversagen trat bei Itraconazol-Patienten merklich weniger auf (25,9 vs. 43,2%). **Schlussfolgerungen:** Die Verträglichkeit von Itraconazol war signifikant höher als beim herkömmlichen AMB. Itraconazol zeigte ebenfalls Vorteile in der Wirksamkeit. Diese Studie bestätigt die Rolle von Itraconazol als sinnvolles und sicheres Medikament in der empirischen antimykotischen Therapie von fiebrigen neutropenischen Tumorpatienten.

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Introduction

Systemic fungal infections represent a major complication for immunocompromised patients with malignant haematological disorders and stem cell transplant (SCT) recipients. Prolonged neutropenia is well recognised as a major risk factor for the development of these infections [1]. The most frequent presentation is persistent fever unresponsive to broad-spectrum antibiotics. The high mortality rates associated with established infection call for empirical antifungal strategies in the management of this high-risk patient group [2]. Several agents with different safety and efficacy profiles are currently used for empirical antifungal therapy. Conventional amphotericin B (AMB) has a broad spectrum of antifungal activity but is associated with serious side effects, in particular nephrotoxicity. New lipid formulations showed comparable efficacy to conventional AMB in randomised controlled trials [3–5] and had a better safety profile than the latter [6]. Second-generation triazoles, (voriconazole and more recently posaconazole) have emerged as suitable antifungal options [7, 8]. In recent years, several clinical studies have investigated the safety and efficacy of another triazole, itraconazole (ITRA), both as oral and intravenous formulation [9, 10]. ITRA proved efficacious both in prophylaxis and treatment of systemic fungal infections in patients with haematological malignancies and SCT recipients (reviewed in e.g. Potter et al. [9]). Intravenous followed by oral ITRA was at least as effective as empirical antifungal therapy in neutropenic febrile cancer patients as AMB and led to significantly fewer drug-related adverse events [10]. In this study, we compared ITRA and AMB in a similar high-risk patient population with special emphasis on safety and tolerability aspects.

Design and Methods

Study Design

This open, randomised, multicentre, parallel-group comparison was conducted at 27 oncology centres in Germany between December 1999 and August 2001. At enrolment, patients were stratified according to allogeneic SCT recipients (stratum 1), subjects with fever of unknown origin (FUO) and lung infiltrates (stratum 2) and FUO patients without lung infiltrates (stratum 3). Central randomisation was performed in blocks of 4. Patients were randomly assigned in a 1:1 ratio to receive either ITRA or AMB. At each centre, balancing ensured that each treatment group was allocated an equal number of subjects.

Independent ethics committees at all the participating institutions approved the study, and all patients provided written informed consent. The study was conducted according to the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice.

Patients

Hospitalised subjects (≥ 18 years of age) with a haematological malignancy treated by myelosuppressive therapy and/or who were allogeneic/autologous bone marrow or blood stem cell transplant recipients were eligible for the study. Other inclusion criteria were a neutrophil count of $< 1.0 \times 10^9$ cells/l expected to last for at least 7 days from the start of the study medication; fever ≥ 38 °C not responding to at least 72 h of broad-spectrum antibiotics – potentially attributable to deep fungal infection – and a life expectancy of at least 14 days. Patients with positive chest X-ray findings (stratum 2) could be randomized as early as the first day of fever, reflecting the higher incidence of fungal infections developing later in the course of this risk category. Patients were excluded if they had previously been entered into this study, participated in an investigational drug trial a week prior to inclusion, or received investigational medication at enrolment. Further exclusion criteria were serum creatinine > 2 times the upper normal limit; serum glutamic pyruvic transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT) ≥ 5 times the upper normal limit; bilirubin ≥ 5 mg/dl; human immunodeficiency virus (HIV)-positive individuals; aplastic anaemia; known hypersensitivity to azole antifungal agents or AMB; and treatment with terfenadine, astemizole, oral midazolam, triazolam, cisapride, HMG-CoA reductase inhibitors, HIV protease inhibitors, quinidine, pimozide, clarithromycin, carbamazepine, isoniazide, phenytoin, rifabutin or rifampicin. Proven deep fungal infection at study entry or during previous episodes of neutropenia, proven systemic bacterial or viral infection at study entry or superficial systemic bacterial or viral infection responsible for the fever, continued treatment with any systemic antifungal therapy (topical agents were allowed) and treatment with AMB within 7 days prior to study entry also led to exclusion. Pregnant or lactating females as well as females without a safe contraception method were not allowed to participate.

Study Medication

Patients received either ITRA or AMB until signs and symptoms were cleared. The maximum treatment period was 28 days. Intravenous ITRA was administered as a 40% hydroxypropyl-ß-cyclodextrin solution in water at a loading dose of 200 mg every 12 h in a 1h-infusion for 2 days followed by 200 mg every 24 h for 12 days. Patients then received an oral solution of ITRA (200 mg) twice daily. However, if patients were able to tolerate oral medication, oral ITRA could replace the intravenous administration earlier.

The recommended dose of AMB was 0.7–1 mg/kg/day. If the subject presented with an X-ray or computed tomography (CT) scan suggestive of fungal infection, the dose could be adjusted to a maximum of 1.5 mg/kg/day. Intravenous administration was preceded by infusion of 500–1,000 ml of 0.9% sodium chloride (NaCl). Treatment could be interrupted if amphotericin toxicity was suspected. In the case of discontinuation of study medication due to poor tolerance, adverse events or deterioration of signs and symptoms, patients could be switched from AMB to ITRA or vice versa for a maximum treatment period of 28 days. This 'follow-up' treatment was analysed separately.

Assessment of Safety and Efficacy

A complete clinical evaluation of the patient's diagnosis, condition and relevant medical and surgical history was carried out at enrolment. Fungal, bacterial and viral surveillance cultures from blood, urine and other suspected sites were taken at study entry and then once weekly. Isolated organisms were identified down to species level. A chest X-ray or CT scan was carried out at study entry and thereafter once weekly; bronchoscopy was conducted if indicated. Body temperature was recorded daily (only highest temperature per day); white blood cell count and neutrophil count every second day. Haematological and biochemical laboratory parameters were determined on days 0, 3, 8, 15, 22 and 28; creatinine clearance was calculated from weight, age and serum creatinine levels on days 0, 3, 8, 11, 15, 18, 22, 25 and 28. Renal toxicity was defined as a doubling or increase of 88 µmol/l in serum creatinine levels from baseline, or a decrease of at least 50% in the calculated creatinine clearance from baseline. All symptoms relating to fungal infection were documented twice per week. All major clinical events during the study period were recorded. If cyclosporin or tacrolimus were administered, plasma levels of both drugs were determined twice weekly. Adverse events and concomitant therapy were monitored daily. Type (defined by WHO ART dictionary) and inci-

Table 1. Definition of evaluation criteria

Criterion	Definition
Failure	documented deep fungal infection or highly suggestive CT scan, with progressive infiltrates death due to fungal infection persistent fever on day 28 deterioration of signs and symptoms potentially attributable to deep fungal infection (whether or not fever disappeared on day 28) empirical antifungal regimen changed by investigator discontinuation of study medication due to poor tolerance (also if treatment period is < 3 days)
Unevaluable	treatment duration < 3 days, except when due to poor tolerance death not due to fungal infection clinically and microbiologically documented bacterial or viral infection alone responsible for the fever
Response	not being classified into the failure or unevaluable category patients who have received 10 days of study medication and remained afebrile for at least 2 consecutive days (< 38 °C)

dence of all adverse events, intensity and relation to study medication were recorded. Assessment was continued as described above during the cross-over period.

The primary objective of the study was to monitor the safety and tolerability of the study medication with the proportion of subjects permanently discontinuing treatment due to any adverse event as the primary parameter. All randomised patients with at least 1 administered dose of study medication were included in this analysis. A global evaluation was carried out by the local investigators in cases of premature discontinuation, at the end of study and after the cross-over period using the criteria 'failure', 'unevaluable' and 'response'. For definitions see table 1.

Secondary objective was the efficacy of the study medication. Efficacy parameters at the end of study were the response rate defined as response / (response + failure + unevaluable), the success rate defined as response / (response + failure), the number of deep fungal infections, the time to response, the time until defervescence, the number of febrile (> 38 °C) days during treatment and the duration of hospitalisation. The study was designed before the EORTC/MSG criteria for the diagnosis of fungal infections were published [11]. The protocol allowed 'patients with CT scan highly suggestive of deep fungal infection [...] and with progressive infiltrates' to be categorized as deep fungal infections even in the absence of microbiological evidence. Baseline infections were those present on or before day 2 of the study, and breakthrough infections those with an onset on day 3 or later. Fungal infections were reviewed by a blinded investigator [A.G.] on the basis of case report form (CRF) data. Parameters were analysed using the intention-to-treat (ITT) population who had at least 1 drug administration and post-baseline efficacy data.

A composite endpoint analysis according to Walsh et al. [5] was performed with slight modifications: overall treatment response was defined as survival for 7 days after the start of treatment, as well as defervescence, successful treatment of any baseline fungal infection, absence of breakthrough invasive fungal infection and no premature discontinuation due to toxicity or lack of efficacy during treatment.

Statistical Analysis

Data management was performed by Quintiles N.V., Louvain-la-Neuve, Belgium, and data analysis was carried out by ClinResearch, Cologne, Germany using the SAS program version 6.12 (SAS Institute Inc., Cary, NC, USA). Treatment equivalence was tested against the alternative that ITRA is superior to AMB with respect to safety. Sample size calculations were therefore based on the proportion of patients who permanently discontinued treatment because of any adverse event. In a recent study, this proportion was 19% in the ITRA group compared to 38% in the AMB group [10]. To detect this difference with 80% power at the two-sided 5% significance level, 87 patients per treatment group were required. To account for a 20% dropout rate, 218 patients were planned to be enrolled.

Baseline demographic group comparison was calculated using Van Elteren's nonparametric test and Cochran-Mantel-Haenszel (CMH) test, both controlled for stratification. The proportion of patients permanently discontinuing treatment due to any adverse event was compared between the groups using CMH and in subgroup analysis using χ^2. The 95% confidence interval (CI) was calculated for the difference in proportions between the treatments. Type and incidence of adverse events were tabulated per treatment group. The Kaplan-Meier estimate was employed for the time until discontinuation of treatment and compared between the groups using the stratified log rank test. For patients whose treatment did not discontinue due to adverse events, time until discontinuation was censored at their last time point. Other safety parameters were analysed descriptively, using the 'last observation carried forward' approach for missing data, if appropriate.

Efficacy parameters were descriptive. Time until defervescence was calculated using the Kaplan-Meier estimate. Differences in response and success rates were calculated with 95% CI using the one-sided Fleiss test for stratified equivalence for the total population and the one-sided Blackwelder test for subgroup analysis. The composite endpoint analysis was performed with Fisher's exact test (one-sided) and 95% CI limits; the 'LOCF' approach for missing data was not used.

Results

Due to slow recruitment, only 166 patients were enrolled into the study. Of those, 162 patients (n = 81 for each treatment group) were included in the safety analysis. As all these patients fulfilled the requirements for ITT analysis, they were all included in the efficacy analysis. 31 patients switched treatment (n = 10 ITRA, n = 21 AMB) and were evaluated for safety and efficacy in the cross-over population.

Table 2 summarises the baseline demographic characteristics of the study population. Both treatment groups compared well. The age group 50–60 years was represented strongest in both groups: 32.1% receiving ITRA, 27.2% receiving AMB. The most common diagnosis was acute myeloid leukaemia (52.2%). Antifungal prophylaxis before start of treatment was given to 66.7% of the patients and consisted of nystatin (1.2% for ITRA, 2.5% for AMB patients), ITRA (9.9% ITRA, 13.6% AMB), fluconazole (45.7% ITRA, 46.9% AMB) and AMB (24.7% ITRA, 27.2% AMB). The mean daily dose of AMB during treatment was 0.79 ± 0.22 mg/kg.

Safety

Study treatment was terminated prematurely for 53.7% of all randomised patients. The main reasons were adverse events (33.3%), subject asymptomatic/cured (6.2%) and insufficient response (4.3%). 5 patients died during treatment (n = 3 ITRA, n = 2 AMB), 20 after completion of treatment (n = 10 in both groups) and 2 after completion of cross-over treatment (n = 1 in each group). Fungal infection with *Candida krusei*

Table 2. Baseline demographics of the study population (n = 162) and stratification data

	Itraconazole (n = 81)	Amphotericin B (n = 81)
Gender (female), %	29.6	32.1[a]
Age, median (range), years	55.0 (18–73)	50.0[b] (18–76)
Underlying diagnosis, patients, %		
Acute lymphatic leukaemia	7.4	14.8
Acute myeloid leukaemia	51.9	53.1
Chronic myeloid leukaemia	12.3	4.9
Lymphoma	17.3	16.0
Myeloma	1.2	2.5
Other	9.9	8.6
Treatment of haematological disease, patients, %		
Total	70.4	71.6
Chemotherapy	29.6	28.4
Allogeneic SCT	14.8	16.0
Autologous SCT	2.5	2.5
PBSCT	23.5	23.5
Stratum, patients, n (%)		
1: Allogeneic SCT	26 (32.1)	24 (29.6)
2: FUO with lung infiltrates	22 (27.2)	33 (40.7)
3: FUO	33 (40.7)	24 (29.6)

[a]p = 0.743.
[b]p = 0.11.
SCT = Stem cell transplant; PBSCT = peripheral blood stem cell transplant; FUO = fever of unknown origin.

Table 3. Most frequent adverse events, n (%) in the two treatment groups; incidence rate > 5%

Adverse event	Itraconazole (n = 81)	Amphotericin B (n = 81)	Total (n = 162)
Increased serum creatinine	1 (1.2)	29 (35.8)	30 (48.6)
Hypokalaemia	5 (6.2)	16 (19.8)	21 (34.0)
Fever	7 (8.6)	13 (16)	20 (32.4)
Vomiting	12 (14.8)	7 (8.6)	19 (30.8)
Rigors	1 (1.2)	16 (19.8)	17 (27.6)
Diarrhoea	11 (13.6)	5 (6.2)	16 (25.9)
Bilirubinaemia	7 (8.6)	6 (7.4)	13 (21.1)
Nausea	8 (9.9)	4 (4.9)	12 (19.4)
Dyspnoea	4 (4.9)	8 (9.9)	12 (19.4)
Skin rash	8 (9.9)	4 (4.9)	12 (19.4)
Increased LDH	7 (8.6)	4 (4.9)	11 (17.8)
Agitation	5 (6.2)	5 (6.2)	10 (16.2)
Increased GGT	3 (3.7)	7 (8.6)	10 (16.2)
Increased BUN	2 (2.5)	7 (8.6)	9 (14.6)

LDH = Lactate dehydrogenase; GGT = gamma glutamyl transferase; BUN = blood urea nitrogen.

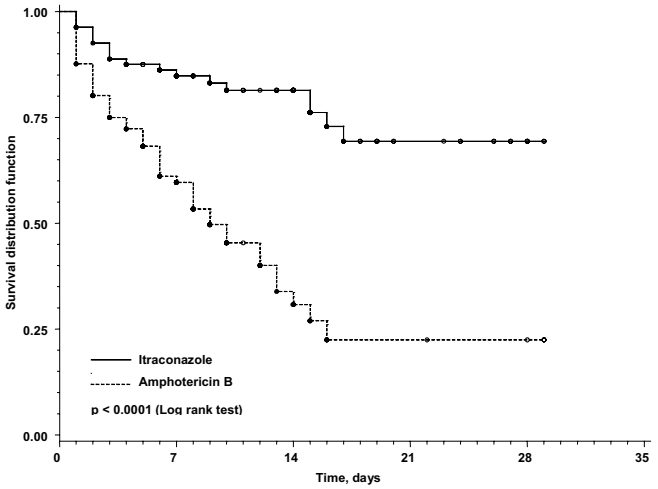

Fig. 1. Time to permanent discontinuation of itraconazole or amphotericin B treatment due to any adverse event for the safety population (n = 162). For patients whose treatment did not discontinue due to adverse events, time until discontinuation was censored at their last time point (ρ At least 1 discontinuation; φ censored only).

caused one death in the ITRA group. Pneumonia and respiratory problems leading to death occurred in 3 of the ITRA patients and 8 of the AMB patients; 2 of the deaths in the AMB group were caused by pulmonary aspergillosis and pneumonia due to *Pseudomonas*, respectively. Multiple organ failure occurred in 1 patient of each group.

Adverse events (independent of a causative relationship to the study drug) during treatment were experienced by 79% in the ITRA and 90.1% in the AMB group. Table 3 lists the most frequent adverse events (incidence rate > 5%). Gastrointestinal complaints and skin rash were more common for ITRA patients, whereas patients receiving AMB experienced more fever episodes, rigor, hypokalaemia and a rise in serum creatinine levels. Adverse events considered as 'very likely' related to the study medication occurred less often in the ITRA (7.4%) compared to the AMB group (51.9%). Severe adverse events occurred in 17.3% of ITRA and 18.5% of AMB patients; the most frequent event originated in the respiratory system (7.4% for each group). More AMB patients had to permanently discontinue treatment due to an adverse event (56.8%) compared to ITRA patients (22.2%; adjusted by strata). This difference was significant (–36 percentage points (95% CI –51.1 to –20.8 percentage points); $p < 0.0001$). The main reasons for withdrawal were increased serum creatinine (1.2% for ITRA vs. 23.5% for AMB) and fever (1.2 vs. 11.1%). Significantly less renal toxicity occurred in ITRA patients (3.7% compared to 40.7% for AMB patients; –39.1 percentage points (95% CI –52.6 to –25.6 percentage points); $p < 0.0001$). Figure 1 shows the time to permanent discontinuation of study medication due to any adverse event for the 2 treatment groups. AMB patients left the study earlier than patients in the ITRA group (9.3 ± 0.7 vs. 14.5 ± 0.6 days, Kaplan-Meier estimate; log-rank test $\chi^2 = 24.36$, $p < 0.0001$, adjusted across strata). A switchover from ITRA to AMB was recorded for 12.3% of patients, from AMB to ITRA for 25.9% of patients.

Table 4. Summary of treatment results

	Itraconazole	Amphotericin B	P value
Discontinued treatment due to any adverse event, %	22.2	56.8	< 0.0001
Average treatment period, days	14.5	9.3	< 0.0001
Response rate, %	61.7	42	< 0.0001
Success rate, %	70.4	49.3	< 0.0001
Composite endpoint (according to Walsh [5]), %	55.1	26.6	0.0002
Fungal infections			
Baseline	4	2	n.s.
Breakthrough[a]	6	6	n.s.

[a]1 in each group based on CT scans only.
n.s. = Not significant.

Efficacy

Overall, 18 fungal infections were observed in the ITT population; 6 were baseline infections with positive cultures within 2 days of study enrolment. Only 1 patient (AMB) was treated for > 3 days and failed; for the other infected patients, treatment was discontinued earlier due to adverse events or lack of efficacy. Breakthrough infections were based in the AMB group on cultures from sterile sites in 3 patients (1 *Aspergillus*, 2 *C. spp.*), and on the combination of bronchoalveolar lavage (BAL) and radiological findings in 2 patients (*C. albicans* and *Aspergillus* plus *C. spp.*). In the ITRA group, breakthrough infections were based on cultures from sterile sites in 3 patients (1 *Aspergillus*, 1 *C. krusei*, 1 *C. spp.*), and on the combination of BAL and radiological findings in 2 patients (1 *Aspergillus*, 1 mixed infection). In 2 patients (1 AMB, 1 ITRA), the diagnosis was based on repeated CT scans only. Given the more stringent EORTC criteria, the latter patients would not have fulfilled the diagnostic criteria of proven or probable infection. Due to the high rate of early cross-over or switch to other available antimycotics, the first positive culture was observed only after termination of the initial treatment in 7/12 cases (5 AMB, 2 ITRA). The results are summarized in table 4.

Time to treatment response was higher for ITRA patients (17.2 ± 0.9 days) than for AMB patients (13.6 ± 1.3 days, mean Kaplan-Meier). The number of febrile days was also slightly higher in the itraconazole group: 5.1 ± 3.8 days compared to 4.1 ± 4.0 days. Defervescence (remaining afebrile for at least 2 consecutive days) was achieved in 69.1% of ITRA patients compared to 60.5% of AMB patients. Median time to defervescence was 4 days for ITRA vs. 3 days for AMB.

Both the response rate and the success rate were in favour of ITRA treatment. The response rate was 61.7% for ITRA compared to 42% for AMB, and the success rate was 70.4% vs. 49.3%. Both differences between the treatment groups were significant ($p < 0.0001$). Failure of treatment occurred more frequently in AMB (43.2%) than in ITRA patients (25.9%).

For the ITT analysis, 50 patients for stratum 1, 55 for stratum 2 and 57 for stratum 3 were available (table 2). A subgroup analysis of the response and success rates in the 3 strata yielded similar results. The response rate was 61.5% ITRA vs. 33.3% AMB (stratum 1; $p = 0.001$), 54.5 vs. 45.5% (stratum 2; $p = 0.038$) and 66.7 vs. 45.8% (stratum 3, $p = 0.003$). For the success rate, the following proportions were found: stratum 1 (69.6 vs. 40%, $p = 0.0015$), stratum 2 (66.7 vs. 55.6%, $p = 0.04$) and stratum 3 (73.3 vs. 50%, $p = 0.002$). All other subgroup analyses revealed safety and efficacy profiles similar to the main analysis.

5 ITT patients could not be included in the composite endpoint analysis, therefore 157 patients were evaluated. The analysis showed an overall response to ITRA for 43 patients (55.1%) and to AMB for 21 patients (26.6%). The difference of 28.55 percentage points (95% CI 13.8–43.3 percentage points) was significant ($p = 0.0002$).

Discussion

ITRA was tolerated significantly better as empirical antifungal therapy in this high-risk patient population than AMB. Although overall mortality was similar for the 2 treatment groups, adverse events were much less frequent in ITRA patients, and only half as many ITRA as AMB patients had to switch treatment. The incidence of infusion-related events was higher in AMB patients. Nearly 20% of these patients experienced rigors. Hypokalaemia and nephrotoxicity were also much less frequent in ITRA compared to AMB patients. Several studies have reported an association of conventional AMB with these side effects. The proportion of patients experiencing hypokalaemia ranged from 11.6 to 48% [5, 10, 12–14] and of those developing nephrotoxicity from 11 to 51.5% [3–5, 10, 12–14] in these studies. The development of metabolic toxicities might require discontinuation of medication. Indeed, the main reason for AMB patients to withdraw from the present study was increased serum creatinine (23.5% compared to 1.2% for ITRA patients), and permanent discontinuation due to any adverse event was significantly higher than in ITRA patients. AMB patients also discontinued study med-

ication earlier. The withdrawal rate for ITRA patients is similar to that found by Boogaerts et al. [10]; the rate for AMB patients was, however, much higher in the present study (38 vs. 56.8%). The assessment of the withdrawal rates according to strata yielded similar results: rates of 62.5, 48.5 and 62.5% were found for the 3 strata, respectively. Drug-related adverse events also occurred less when administering ITRA (the proportions were similar to Boogaerts et al [10]); severe adverse events, however, occurred twice as often in their amphotericin group than in our study. The most favourable safety aspect of ITRA was the near absence of renal toxicity. Only 3.7 vs. 40.7% of AMB patients experienced renal toxicity. This translates into an advantage of treatment with ITRA in patients with existing or developing renal insufficiency as well as in patients requiring concomitant treatment with other nephrotoxic agents such as aminoglycosides or cyclosporin. A reduced risk of renal toxicity was established in a recent systematic review for lipid-based amphotericin formulations but efficacy proved to be similar to conventional AMB [6].

The incidence of systemic infection was low and occurred at a similar rate in both treatment groups. A similar proportion of patients achieved defervescence. The higher efficacy of ITRA at similar time to defervescence can be based on the rate of complications under AMB treatment.

ITRA proved more efficacious than AMB in this study. Both the response and success rates were significantly higher, and treatment failure was markedly reduced when ITRA was administered. Overall response according to composite endpoint analysis was seen in twice as many ITRA patients (43 vs. 21). The overall response to ITRA of 55.1% confirms the data of Boogaerts et al. (53% [10]), but the outcome for AMB was much lower in the present study (26.6 vs. 46%). Treatment failure was less frequent in our study. The subgroup analysis showed no difference in treatment response or tolerability of the study medication between the 3 strata. ITRA compared favourably to AMB in all 3 patient groups. Rates of fungal infections were not a primary endpoint of the study but were comparable in both groups. Due to the small number of patients finishing the initial therapy, successful therapy of baseline or emerging infections cannot be evaluated. One has to keep in mind that the superior efficacy of ITRA is based exclusively on superior tolerability in this study.

Our results are limited by the open-label design of the study. The fact that investigators were not blinded to study medication might have biased the reporting of drug-related adverse events and treatment response. This makes it impossible to compare the composite endpoint percentages across studies. It should also be noted that the study was powered for safety and not for efficacy.

Newer and more costly drugs continue to be evaluated for proven infection [15] and in the empirical setting [16]. In the absence of comparative studies, only indirect conclusions of comparative merits both in antifungal efficacy, side effects and cost efficiency can be derived. ITRA shares the obvious advantage of oral availability with voriconazole but does not show the side effect of altered vision. Despite the compelling data in proven infection [15], data in support of voriconazole in the empirical setting were less favourable [7]. On this basis, voriconazole has not yet been approved for empirical therapy in several countries. Caspofungin is another tempting alternative [16], however, in comparison to ITRA the considerably higher price limits its administration to more highly selected patients.

In conclusion, our results have confirmed a role of ITRA as a safe and efficacious alternative to conventional AMB as empirical antifungal therapy for neutropenic fever in patients with haematological malignancies.

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