ELSEVIER

International Journal of Antimicrobial Agents 31 (2008) 135–141

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Safety of a weekly high dose of liposomal amphotericin B for prophylaxis of invasive fungal infection in immunocompromised patients: PROPHYSOME Study

Catherine Cordonnier [a,*], Mohamad Mohty [b], Catherine Faucher [b], Cécile Pautas [a], Marie Robin [c], Norbert Vey [b], Françoise Monchecourt [d], Lamine Mahi [d], Patricia Ribaud [c]

[a] *Hôpital Henri Mondor, Créteil, France*
[b] *Institut Paoli-Calmettes, Marseille, France*
[c] *Hôpital Saint-Louis, Paris, France*
[d] *Gilead Sciences, Paris, France*

Received 11 June 2007; accepted 1 October 2007

Abstract

With its broad spectrum of activity and better tolerability profile than conventional amphotericin B, liposomal amphotericin B (L-AmB) may be the drug of choice for antifungal prophylaxis in haematological patients. An open-label, multicentre, prospective, pilot study was conducted in adult patients receiving chemotherapy for acute leukaemia (AL) or myeloablative allogeneic stem cell transplantation (SCT). Patients received weekly 10 mg/kg infusions of L-AmB for 4 weeks for AL and 8 weeks for SCT. The primary objective was safety, with particular attention to infusion-related reactions and nephrotoxicity. Twenty-nine adult patients were included: 21 AL (median age 52 years) and 8 SCT (median age 37 years). The most frequent adverse events (AEs) related to study drug were infusion-related reactions, 12 of which (from a total of 76 infusions) led to increased infusion duration for better tolerance. No AE related to the study drug led to discontinuation of prophylactic treatment in AL patients. In SCT patients, eight AEs (in six patients) reported to be related to study treatment led to treatment discontinuation. Enrolment was discontinued in the SCT group as recommended by the independent data review committee in accordance with the 10% limit of AEs (CTC grade 3–4) fixed by the protocol. The appropriate timing of high-dose prophylactic L-AmB remains to be determined in the SCT setting to optimise the safety profile of this regimen. For AL, a 10 mg/kg weekly dose appears to be well tolerated during chemotherapy and may represent an important tool towards improving AL patient outcome.

Keywords: Liposomal amphotericin B; Antifungal prophylaxis; Invasive fungal infection

1. Introduction

The increased number of allogeneic stem cell transplantations (SCTs), and consequently the increased number of patients with graft-versus-host disease (GvHD), is associated with a higher frequency of invasive fungal infections (IFIs) mainly caused by *Aspergillus* and *Candida* spp. [1]. The annual incidence of invasive aspergillosis (IA) has been reported at 10.5% among recipients of HLA-mismatched or unrelated donor transplants and 7.3% among recipients of matched, related donor transplants [2]. Despite improvements in antifungal therapy, the 1-year overall survival after diagnosis of IA in SCT patients does not exceed 30% [2,3]. Similarly, acute leukaemia (AL) patients undergoing high-dose remission-induction chemotherapy also have an increased incidence of fatal IFIs. Although the latter may depend on the antileukaemic regimen, this incidence may reach 36% in patients treated with high-dose cytarabine [4].

With this background, prophylactic treatments have been widely used to prevent IFIs [5]. Fluconazole prophylaxis was found to reduce the incidence of superficial and invasive

* Corresponding author. Present address: Service d'Hématologie Clinique, Hôpital Henri Mondor, 94000 Créteil, France. Tel.: +33 1 49 81 20 59; fax: +33 1 49 81 20 67.
E-mail address: carlcord@club-internet.fr (C. Cordonnier).

0924-8579/$ – see front matter © 2007 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.
doi:10.1016/j.ijantimicag.2007.10.001

candidiasis in SCT recipients, thereby improving long-term survival [2,6]. However, fluconazole has no activity against moulds such as *Aspergillus* spp. Itraconazole, micafungin and posaconazole are alternatives to fluconazole prophylaxis [7–10].

In haematological patients, amphotericin B (AmB) has the broadest spectrum of activity of all available antifungal agents. However, prophylactic use of conventional AmB at the usual dosage is hampered by its nephrotoxicity. Prophylactic trials with low doses of AmB deoxycholate did not show clinical benefit over placebo or fluconazole [11,12]. Higher doses of AmB deoxycholate (1 mg/kg every 48 h) were used by Karthaus et al. [13] for prophylaxis in AL patients, with moderate rates of nephrotoxicity and infusion-related adverse events (AEs). However, the outcome for this group of patients was only compared with a historical group. Thus far, no large, placebo-controlled trials have evaluated the efficacy of AmB for primary prophylaxis [14]. Use of the liposomal form of AmB (L-AmB) appears to be more promising owing to its lower toxicity compared with AmB deoxycholate [15]. In this perspective, Tollemar et al. [16–18] studied the administration of L-AmB (1 mg/kg/day) to a small population of allogeneic SCT patients. No significant differences were found compared with the placebo arm. The comparative placebo-controlled study of Kelsey et al. [19] was performed with L-AmB using a dose of 2 mg/kg three times weekly in patients undergoing chemotherapy or SCT. These authors concluded that this prophylactic treatment reduced the incidence of fungal colonisation, with a good safety profile. However, there was no significant reduction in the incidence of IFI or antifungal therapy requirements. In all the latter studies evaluating prophylactic use of L-AmB, the absence of clinically significant efficacy may have been due to low statistical power. Further assessment of the benefit of IFI prophylaxis using L-AmB is justified by the unique pharmacokinetics of L-AmB. Indeed, this galenic form could be of great value in a prophylactic setting since L-AmB exhibits non-linear pharmacokinetics (maximal serum concentration (C_{max}) and area under the concentration–time curve (AUC) at 10 mg/kg) with differential tissue uptake: the drug accumulates preferentially in organs of the reticuloendothelial system (RES) [15]. Therefore, high doses are required to overcome RES uptake and the drug accumulates in greater concentrations in lung tissue. This has been demonstrated both in animal models and humans. For instance, in a murine model of *Aspergillus* infection, AmB was measured in tissue and blood at an effective concentration 7 days after injection of a single dose of AmB [20]. Furthermore, Gubbins et al. [21] showed in adult patients undergoing autologous SCT that infusion of a single 15 mg/kg dose of L-AmB was well tolerated and achieved high tissue concentrations. The safety of weekly high doses of L-AmB has also recently been confirmed in children undergoing SCT [22].

With once-weekly infusion, the absence of an oral form for L-AmB is less of a disadvantage for long-term use. Moreover, a unique weekly dose is likely to be more acceptable to the patient and medical team in the context of complex management and many scheduled treatments.

The aim of this prospective pilot study was to assess the safety and tolerability of L-AmB given once weekly at a high dose (10 mg/kg) as antifungal prophylaxis in patients undergoing SCT or receiving induction or consolidation chemotherapy for AL.

2. Patients and methods

2.1. Study design

This was a prospective, pilot, phase II multicentre study. Two groups of patients were enrolled: (i) patients with AL undergoing induction chemotherapy (initial induction or following relapse) or consolidation high-dose chemotherapy; and (ii) patients undergoing standard myeloablative conditioning for allogeneic SCT and receiving cyclosporin A for GvHD prophylaxis. Patients with AL were treated with L-AmB for 4 weeks and patients with SCT for 8 weeks. No other systemic antifungal prophylaxis was allowed to be used concomitantly.

Patients were enrolled between March 2004 and March 2006 in three centres in France. Written informed consent was obtained from each patient before any study procedure.

2.2. Patient population

Patients were eligible for the study if they were ≥18 years old, underwent a standard myeloablative conditioning regimen and acute GvHD cyclosporin prophylaxis for SCT or underwent first or second induction therapy after relapse or consolidation therapy for AL and had expected neutropenia $<0.5 \times 10^9$ neutrophils/L for at least 2 weeks. In addition, patients had to have a normal chest computed tomography (CT) scan and/or normal chest radiograph at baseline, with no signs or symptoms of fungal infection and no prior history of proven or probable IFI. The main exclusion criteria were: known hypersensitivity to AmB; cord blood transplantation; creatinine clearance <60 mL/min; moderate or severe liver disease defined by a five-fold increase in the upper limit of normal of hepatic enzymes; limited life expectancy (<1 month); fever (≥38.5 °C); previous treatment with systemic antifungal therapy within 15 days before inclusion; severe cardiovascular disease; severe disease (other than haematological disease); and pregnancy or nursing.

2.3. Administration of the study drug

Patients received intravenous L-AmB (Gilead Sciences, Inc., Foster City, CA) at 10 mg/kg once a week (4 consecutive weeks for AL patients and 8 consecutive weeks for SCT patients). The first administration was given within 48 h before or after chemotherapy initiation. The study drug was

administered intravenously over 2 h under medical supervision. For subsequent infusions, the attending physician was allowed to administer premedication (paracetamol and dexchlorpheniramine only) in patients who had experienced infusion-related AEs during the first infusion.

2.4. Assessment of patients

Safety was assessed by the rate of AEs occurring during the course of prophylaxis treatment. Laboratory tests were performed every 2 days from baseline to Day 15 and then once a week: haematology (blood counts); and biochemistry (serum creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, sodium, potassium, phosphate, calcium, magnesium and glucose). A urinary ionogram was also performed once a week. A serious AE was defined as any AE that resulted in death, a life-threatening situation, hospitalisation or prolongation of existing hospitalisation (excluding those for study therapy), persistent or significant disability/incapacity or other important medical event according to the investigator's judgment. An independent data review committee composed of a haematologist, an infectious diseases specialist and a statistician assessed all safety results. The maximal acceptable rate of AEs had been previously defined in the study protocol as 10%. Safety and tolerability were assessed according to the incidence of grade 3–4 AEs based on the Common Toxicity Criteria (CTC) classification, reported as definitely, possibly or probably related to the study drug [23].

Efficacy was assessed by physical examination, weekly cultures (swabs from the nose and oropharynx, blood, stool and urine) and twice weekly serum *Aspergillus* galactomannan enzyme immunoassay. When clinically relevant, CT or radiography of the chest and abdomen, bronchoalveolar lavage and biopsy of suspicious lesions/sites with microscopic evaluation and cultures were done at the discretion of the investigator. Diagnosis of IFI was done according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [24].

2.5. Statistical analysis

The primary endpoint was safety, defined by the incidence of AEs occurring during the course of prophylactic treatment. The main secondary endpoints were related to prophylaxis efficacy (incidence of probable or proven IFI) within the course of the prophylaxis period or during the 24-week follow-up after the initiation of treatment. Incidence of fever of unknown origin requiring empirical antifungal treatment during the prophylaxis period, survival rate and incidence of mortality related to IFI within 24 weeks were also assessed. Considering that the main objective of this pilot study was safety and feasibility, it was arbitrarily planned to enrol *ca.* 30 patients to achieve 24 patients for analysis.

Table 1
Clinical characteristics of the patients at inclusion

Characteristics	AL patients ($N=21$)	SCT patients ($N=8$)
Men/women (n)	12/9	5/3
Median age (range) (years)	52 (38–63)	37 (23.5–42.5)
Underlying condition (n)		
Acute myeloblastic leukaemia	19	1
Acute lymphoblastic leukaemia	2	3
Chronic myeloid leukaemia	0	3
Myeloproliferative disorder	0	1
Allogeneic stem cell transplant		
HLA-identical sibling donor	N/A	5
Unrelated donor	N/A	3

AL, acute leukaemia; SCT, stem cell transplantation; N/A, not applicable.

3. Results

3.1. Patients characteristics at baseline

The baseline characteristics of the 29 patients included in the study are presented in Table 1. The majority of patients were male and the median age was 52 years (range 38–63 years) for AL patients and 37 years (range 23.5–42.5 years) for SCT patients. Allogeneic SCT recipients received a myeloablative conditioning regimen, either with cyclophosphamide and total body irradiation ($n=4$) or cyclophosphamide and busulfan ($n=3$) (data missing for 1 patient). Most AL patients had acute myeloblastic leukaemia (19/21) (Table 1). Seventeen (81%) of 21 patients received the study drug while receiving induction chemotherapy, whereas the remaining 4 patients (19%) received it during high-dose consolidation.

3.2. Duration of therapy

All patients included received at least the first prophylactic dose. The median duration of the first infusion was 2 h for AL patients and 2.25 h for SCT patients. The median duration of prophylaxis treatment was 20 days for AL patients (median of three infusions per patient) and 7 days for SCT patients (median of one infusion per patient).

3.3. Safety assessment during prophylactic treatment

Particular attention was paid to nephrotoxicity and infusion-related reactions. During the prophylaxis period, all patients reported at least one AE. The main study drug-related CTC grade 3–4 AEs reported by the investigators are detailed in Table 2. Because the rate of CTC grade 3–4 AEs was above the 10% limit fixed by the protocol, it was decided by the independent data review committee to stop the inclusion of SCT subjects.

Renal and electrolyte disorders were frequent (Table 3). However, they were frequently unrelated to the prophylactic treatment. The latter may be explained by the fact that all

Table 2
Common Toxicity Criteria (CTC) grade 3–4 adverse events (AEs) related to prophylactic treatment

	AL patients ($N=21$)	SCT patients ($N=8$)
No. of infusions by group	64	12
Median no. of infusions by patient (min; max)	3 (1; 4)	1 (1; 3)
No. of AEs (all CTC grades) related to prophylactic treatment	21	12
No. of patients with > 1 AE (all CTC grades) related to prophylactic treatment	14	6
CTC grade 3–4 AEs related to prophylactic treatment	2	6
Hypokalaemia	2	0
Dyspnoea	0	1
Thoracic pain	0	1
Abdominal pain	0	1
Tubulointerstitial nephritis	0	1
Anuria	0	1
Anaphylactic shock	0	1

AL, acute leukaemia; SCT, stem cell transplantation.

patients received at least one concomitant nephrotoxic medication. Of note, all SCT patients received cyclosporin A. Analysis of serum creatinine values up to 1 month after the last infusion demonstrated an increase ≥2-fold the baseline value in 2/21 AL patients and 2/8 SCT patients.

Other AEs led to modification of infusion conditions (Table 4). Overall, for a total of 76 infusions, 12 AEs (mainly hot flushes, chills and allergic reactions) reported from nine patients led to an increased infusion duration for better tolerance.

Discontinuation of prophylactic treatment occurred in three AL patients (14%) owing to four AEs (fever, bronchopulmonary aspergillosis, *Escherichia coli* sepsis and positive *Candida* serology); none of these AEs were related to study treatment. Discontinuation of prophylactic treatment occurred in eight SCT patients (100%) owing to 11 adverse events: 3 were not related to study treatment (renal insufficiency, thrombotic microangiopathy and bronchopulmonary aspergillosis) and 8 were reported to be related to study treatment (dyspnoea, chest pain, abdominal pain, nausea, tubulointerstitial nephritis, renal insufficiency, anuria and anaphylactic shock).

Table 3
Renal and hydroelectrolytic disorders observed during the study, irrespective of their relationship to the study drug

	AL patients ($N=21$)	SCT patients ($N=8$)
No. of patients with at least one nephrotoxic drug	21	8
No. of patients with at least one renal or hydroelectrolytic disorder	19	6
Renal and hydroelectrolytic disorders related to study drug/total	3/39	4/13
Hypokalaemia	2/12	0/1
Fluid retention	0/13	0/3
Serum creatinine increase	1/9	1/4
Others[a]	0/5	3/5

AL, acute leukaemia; SCT, stem cell transplantation.
[a] Tubulointerstitial nephritis (0 and 1 related for AL and SCT patients, respectively), nephrotic syndrome (0 and 1 unrelated), tubular disorder (1 unrelated and 0), hyperkalaemia (2 unrelated and 1 unrelated) and anuria/dysuria (2 unrelated and 2 related).

Table 4
Infusion-related adverse events (AEs) that modified infusion conditions

	AL patients ($N=21$)	SCT patients ($N=8$)
Total no. of infusions	64	12
No. (%) of patients with > 1 AE that caused increase of infusion duration	8 (38%)	1 (13%)
AEs that caused increase of infusion duration for better tolerance[a]	11	1
Hot flush	3	0
Chills	2	0
Anaphylactic shock, hypersensitivity	2	0
Others[b]	4	1

AL, acute leukaemia; SCT, stem cell transplantation.
[a] Present and/or next infusion.
[b] Fever (1 and 0 for AL and SCT patients, respectively), chest discomfort (1 and 0), toxic skin eruption (1 and 0), anxiety (1 and 0) and vomiting (0 and 1).

In the AL group, 16 serious AEs were reported for ten patients, whilst 8 serious AEs were reported for four SCT patients. Two serious AEs (anuria CTC grade 4 and anaphylactic shock CTC grade 3), both in the SCT group, were considered as related to the prophylactic antifungal treatment.

Two episodes of hypokalaemia (CTC grade 3) were reported and were thought to be related to the study drug in the AL group. These two patients rapidly recovered after symptomatic treatment.

3.4. Onset of antifungal empirical treatment during the prophylaxis period

Thirteen AL patients and four SCT patients received antifungal empirical treatment during the prophylaxis period. The median time to first empirical antifungal treatment was 17 days in AL patients and 7.5 days for SCT patients (Table 5).

3.5. Survival of patients

Four deaths (two AL patients and two SCT patients) occurred during the study (prophylaxis period and follow-up period); only one death (SCT patient) was attributed to IFI (probable cerebral aspergillosis); other IFIs that occurred during the study (three AL patients and one SCT patient) are described in Table 5.

4. Discussion

The aim of the present trial was to investigate the safety and feasibility of a high dose of L-AmB (10 mg/kg) administered

Table 5
Administration of antifungal empirical treatment, invasive fungal infections (IFIs) and survival during the study period (intention-to-treat population)

	AL patients ($N = 21$)	SCT patients ($N = 8$)
No. (%) of patients with empirical antifungal treatment[a]	13 (62)	4 (50)
Median time to first empirical antifungal treatment (Q1; Q3) (days)	17 (11; 20)	7.5 (5; 12.5)
Diagnosis of probable or proven IFI[b] (*n*)	3[c]	1[d]
Survival status at the end of the follow-up period (24 weeks)	13/15 (87%)	6/8 (75%)
Deaths[e]	2	2

AL, acute leukaemia; SCT, stem cell transplantation.
[a] During the prophylaxis period.
[b] During the 24-week period after prophylaxis initiation.
[c] One probable candidiasis, one probable aspergillosis and one proven aspergillosis according to EORTC-MSG criteria.
[d] One probable aspergillosis.
[e] Two deaths at Day 41 (septic shock) and Day 149 (drug ineffective) after study drug initiation in the AL group and two deaths at Day 85 (probable cerebral aspergillosis) and Day 131 (acute respiratory failure) in the SCT group.

once weekly for antifungal prophylaxis. This new therapeutic approach is supported by previous pre-clinical and pharmacokinetic studies that suggested the relevance of a high-dose regimen of L-AmB in the prophylaxis of fungal infections. Indeed, in healthy volunteers L-AmB has a long half-life (*ca.* 152 h) [25]. Moreover, a murine model of fungal infection demonstrated that a single dose of L-AmB (5–20 mg/kg) had prophylactic efficacy in murine systemic candidiasis and histoplasmosis [26]. In this study, a weekly 10 mg/kg dose was selected since previous results indicated that dosages of L-AmB as high as 15 mg/kg/day were well tolerated (despite a relatively high rate of hypokalaemia) in patients with IFI with an AUC maximised at 10 mg/kg/day [15].

The stringent acceptable limit for AEs fixed by the protocol revealed a possible safety issue that emerged from this study in SCT patients. Indeed, in the course of the study the number of patients with AEs (CTC grade 3 or 4 related to the study drug) was in excess of the 10% limit fixed by the protocol. In this regard, the number of study drug-related AEs was 21 for AL patients and 12 for SCT patients for a total of 64 and 12 infusions, respectively. Moreover, L-AmB was frequently discontinued in the SCT group as soon as the first infusion (4/8 patients) but not in the AL group. Based on these results, enrolment was discontinued in the SCT group as recommended by the independent data review committee in accordance with the strict 10% limit fixed by the protocol. Nevertheless, the AL patients completed up to 21 infusions.

Factors specific to the SCT patients could have favoured the occurrence of AEs, such as the high use of nephrotoxic drugs. Such difficulties related to safety evaluation of antifungal treatments have already been underlined in the recommendations for antifungal treatment evaluation issued by the European Agency for Evaluation of Medicinal Products (EMEA) [27]. Indeed, owing to the serious underlying condition and numerous concomitant medications, the drug-relatedness of AEs is difficult to establish in such haematological patients.

This pilot study pointed out the possible difficulties for SCT patients starting this type of prophylactic treatment just before or after a conditioning regimen. According to our protocol, the first infusion should be given within a time interval of 48 h before or after chemotherapy initiation. However, the median time between Day 1 of conditioning and Day 1 of prophylaxis was 3 days. Our safety results in the SCT population partly contrast with previous studies that did not meet safety issues at similar doses [15]. Several hypotheses may be proposed to explain these differences. First, these studies with high-dose L-AmB were run in therapeutic settings and the relationship between any AE and the study drug may have been more difficult to establish in complex patients receiving numerous concomitant medications. Second, AEs may be better accepted by investigators when obvious therapeutic benefit is expected, rather than in the setting of an open investigational study. Future protocols should anticipate this potential safety issue, which is expected to be a determining factor for optimal prophylactic treatment. Thus, in a recent pilot study with 21 SCT recipients who received 7.5 mg/kg/week of L-AmB, such side effects were not observed, likely because of a different timing of administration [28]. The patients received the study drug at time of GvHD, and steroids were administered long after the conditioning regimen.

In AL patients, the most frequent AEs related to the study drug were reported during infusion and led to an increase of infusion time in order to improve tolerance. In addition, patients from the AL group frequently had to discontinue the study drug because administration of empirical antifungal treatment was needed. However, administration of empirical treatment *per se* should not be considered as a failure of prophylactic therapy as long as no proven or probable IFI was documented. As far as the indication of empirical antifungal therapy is a standard practice, the optimal antifungal strategy should be considered as a continuum including prophylaxis followed by empirical treatment.

Since the initiation of the present trial, recent studies have confirmed the good tolerance of high doses of L-AmB. The recent clinical study by Mehta et al. [22] investigated the pharmacokinetics and safety of once-weekly high-dose L-AmB therapy in young children undergoing SCT. L-AmB was well tolerated at this dose and was measurable in plasma 7 days after high-dose infusion. After 7 days, the concentration of AmB was near the minimum inhibitory concentration for susceptible strains [29]. The study by Gubbins et al. [21] in adult patients undergoing SCT showed that infusion of a single 15 mg/kg dose of L-AmB achieved similar levels in tissues 7 days after the infusion compared with those obtained with daily 1 mg/kg doses. Moreover, the ratio of tissue/blood AmB levels was 16.3, thus indicating that a single high dose of AmB was well tolerated and achieved high tissue concentration. This tissue accumulation supports the prophylactic use

of L-AmB with weekly high-dose administration and could explain the non-linear pharmacokinetics observed in the previous study of Walsh et al. [15]. The dose escalation study of Walsh et al. with L-AmB doses up to 15 mg/kg in patients with fungal infections showed that for doses above 10 mg/kg, C_{max} and AUC did not further increase. It is thought that uptake of L-AmB by the RES with accumulation of AmB in tissues explain this unique pharmacokinetics. Thus, safety, pharmacokinetic characteristics and tissue accumulation argue for the use of L-AmB as prophylactic antifungal treatment. Clinical studies such as the present trial should help to optimise the choice of prophylactic treatment, timing and dosage to prevent fungal infection in immunocompromised patients.

In conclusion, the aim of this pilot study was to demonstrate the safety and feasibility of a weekly prophylactic treatment with L-AmB at high dose in a high-risk population. In SCT patients who were receiving multiple concomitant nephrotoxic drugs, it appears that the appropriate timing and dose for the initiation of a prophylactic high dose of L-AmB may remain to be determined in order to optimise the safety profile of this regimen. However, this treatment was well tolerated during induction or consolidation chemotherapy for AL, warranting further prospective testing in this setting. Considering the broad spectrum of L-AmB, evaluation of its prophylactic efficacy with this mode of administration deserves comparison with the more recent azoles evaluated in this setting.

Acknowledgments

The authors thank the members of the independent data review committee, A. Thiébaut, B. Gachot and J.M. Grouin; the nursing staff of the three sites involved; and F. Beauvais, A. Duvivier and B. Bonnet (Gilead Sciences France) for their support and assistance.

Funding: Gilead Sciences France.

Competing interests: CC has received grants and research support from Pfizer, Merck Sharp & Dohme–Chibret, Gilead and Schering-Plough and has been a consultant for Gilead, Schering-Plough and Zeneus Pharma. PR is a member of the speakers' bureau for Pfizer, Merck and Schering-Plough. CP, MR, MM, CF and NV have no disclosures to make in relation to this manuscript. FM and LM are Gilead employees.

Ethical approval: The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the ethical committee ('Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale') of Créteil Hôpital Henri Mondor, France. ClinicalTrials.gov Identifier: NCT00362544.

References

[1] Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997;175:1459–66.

[2] Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002;100:4358–66.

[3] Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis 2007;44:531–40.

[4] Bow EJ, Loewen R, Cheang MS, Schacter B. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. Clin Infect Dis 1995;21:361–9.

[5] Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with hematologic malignancies. Blood 2003;101:3365–72.

[6] Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J Infect Dis 1995;171:1545–52.

[7] Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348–59.

[8] Glasmacher A, Prentice A, Gorschlüter M, Engelhart S, Hahn C, Djulbegovic B, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol 2003;21:4615–26.

[9] Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356:335–47.

[10] van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004;39:1407–16.

[11] Perfect JR, Klotman ME, Gilbert CC, Crawford DD, Rosner GL, Wright KA, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. J Infect Dis 1992;165:891–7.

[12] Wolff SN, Fay J, Stevens D, Herzig RH, Pohlman B, Bolwell B, et al. Fluconazole vs low-dose amphotericin B for the prevention of fungal infections in patients undergoing bone marrow transplantation: a study of the North American Marrow Transplant Group. Bone Marrow Transplant 2000;25:853–9.

[13] Karthaus M, Doellmann T, Klimasch T, Elser C, Rosenthal C, Ganser A, et al. Intensive intravenous amphotericin B for prophylaxis of systemic fungal infections. Results of a prospective controlled pilot study in acute leukemia patients. Chemotherapy 2000;46:293–302.

[14] Bow EJ. Long-term antifungal prophylaxis in high-risk hematopoietic stem cell transplant recipients. Med Mycol 2005;43(Suppl. 1):S277–87.

[15] Walsh TJ, Goodman JL, Pappas P, Bekersky I, Buell DN, Roden M, et al. Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with *Aspergillus* species and other filamentous fungi: maximum tolerated dose study. Antimicrob Agents Chemother 2001;45:3487–96.

[16] Tollemar J, Hockerstedt K, Ericzon BG, Sundberg B, Ringden O. Fungal prophylaxis with AmBisome in liver and bone marrow transplant recipients: results of two randomized double-blind studies. Transplant Proc 1994;26:1833.

[17] Tollemar J, Ringdén O, Andersson S, Sundberg B, Ljungman P, Sparrelid E, et al. Prophylactic use of liposomal amphotericin B (AmBisome) against fungal infections: a randomized trial in bone marrow transplant recipients. Transplant Proc 1993;25:1495–7.

[18] Tollemar J, Ringden O, Andersson S, Sundberg B, Ljungman P, Tyden G. Randomized double-blind study of liposomal amphotericin B (Ambisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. Bone Marrow Transplant 1993;12:577–82.

[19] Kelsey SM, Goldman JM, McCann S, Newland AC, Scarffe JH, Oppenheim BA, et al. Liposomal amphotericin (AmBisome) in the

prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study. Bone Marrow Transplant 1999;23:163–8.

[20] te Dorsthorst DT, Verweij PE, Meis JF, Mouton JW. Efficacy of one-day versus seven-day AmBisome treatment in a non-neutropenic murine model of invasive aspergillosis. In: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 30 October–2 November 2004; Washington, DC. Abstract A1873.

[21] Gubbins PO, McConnell SA, Amsden JR, Anaissie E. Comparison of liposomal amphotericin B plasma and tissue concentrations following a single large (15 mg/kg) dose or daily 1 mg/kg dosing. In: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 30 October–2 November 2004; Washington, DC. Abstract A33.

[22] Mehta P, Vinks A, Filipovich A, Vaughn G, Fearing D, Sper C, et al. High-dose weekly AmBisome antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: a pharmacokinetic study. Biol Blood Marrow Transplant 2006;12: 235–40.

[23] Cancer Therapy Evaluation Program. Common Toxicity Criteria Version 2.0. DCTD, NCI, NIH, DHHS March 1998. Cancer Therapy Evaluation Program; 1998.

[24] Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7–14.

[25] Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. Antimicrob Agents Chemother 2002;46:828–33.

[26] Garcia A, Adler-Moore JP, Proffitt RT. Single-dose AmBisome (Liposomal amphotericin B) as prophylaxis for murine systemic candidiasis and histoplasmosis. Antimicrob Agents Chemother 2000;44:2327–32.

[27] European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products (CPMP). Points to consider on the clinical evaluation of new agents for invasive fungal infections. London, UK: CPMP; 2003. http://www.emea.eu.int/pdfs/human/ewp/134301en.pdf [accessed 17 October 2007].

[28] El-Cheikh J, Faucher C, Fürst S, Duran S, Berger P, Vey N, et al. High-dose weekly liposomal amphotericin B antifungal prophylaxis following reduced-intensity conditioning allogeneic stem cell transplantation. Bone Marrow Transplant 2007;39:301–6.

[29] Andes D. Clinical utility of antifungal pharmacokinetics and pharmacodynamics. Curr Opin Infect Dis 2004;17:533–40.