available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Primary antifungal prophylaxis in leukaemia patients ☆

Johan A. Maertens[a,*], *Pascale Frère*[b], *Cornelia Lass-Flörl*[c], *Werner Heinz*[d], *Oliver A. Cornely*[e]

[a]*Department of Haematology, Leukaemia and Stem Cell Transplantation Unit, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[b]*Department of Medicine, Division of Haematology, University of Liege, Liege, Belgium*
[c]*Department of Hygiene and Medical Microbiology, Medical University of Innsbruck, Austria*
[d]*Medizinische Klinik und Poliklinik II, Division of Infectious Diseases, University of Würzburg, Würzburg, Germany*
[e]*Klinik I für Innere Medizin, Klinische Infektiologie, Köln, Germany*

ARTICLE INFO

Article history:
Received 14 May 2007
Received in revised form 11 June 2007
Accepted 12 June 2007

Keywords:
Prophylaxis
Antifungal
Neutropenia
Leukaemia
Stem cell transplantation
Candida
Aspergillus

ABSTRACT

These recommendations have been developed by an expert panel following an evidence-based search of the literature assessing the role of primary antifungal prophylaxis in patients with acute leukaemia or stem cell transplantation. We present results from a questionnaire on the current practice among experts in Europe, show results of the literature search and provide the panel's recommendations.

1. Introduction

Patients with acute leukaemia (AL) or myelodysplastic syndrome (MDS) who undergo successive cycles of myelosuppressive chemotherapy or who undergo haematopoietic stem cell transplantation (HSCT) have a high incidence of proven and probable mould and yeast infections. Treatment of these infections is often ineffective due to delays in diagnosis, resulting in high mortality rates.[1–3] Besides, signs and symptoms of infection are usually non-specific and these infections are commonly missed by culture or because of the inability to perform biopsies.[4] Consequently, primary antifungal chemoprophylaxis (PAC) has been recommended and has become routine practice in many European Leukaemia and HSCT centres.[5] However, in spite of the burden of published data on PAC, drawing solid scientific conclusions remains challenging.[6] This highlights the need for evidence-based European recommendations.

☆ The ECIL 1 is a common initiative of the following groups or organisations: European Blood and Marrow Transplantation Group, European Organisation for Treatment and Research of Cancer, European Leukemia Net (EU Grant LSHC-CT-2004) and Immunocompromised Host Society.

* *Corresponding author:* Tel.: +32 16 34 68 80; fax: +32 16 34 68 81.
E-mail address: johan.maertens@uz.kuleuven.ac.be (J.A. Maertens).

1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2007.06.006

2. Methods

The European Conference on Infections in Leukaemia (ECIL) recommendations on PAC are based on a review of the English-language literature following a predefined methodology (see introductory chapter) and using the following key words: neutropenia, stem cell transplantation, azole, prophylaxis, antifungal, prevention, fungal infection and aspergillosis.

Many of the published studies were observational or used historical controls. Such approaches, even when properly matched, are inevitably biased. We therefore decided that preferably prospective, randomised trials would be considered for efficacy assessment (quality of evidence, level I). Drawing firm conclusions remained challenging, however, given the non-blinded nature of many of these studies and the risk of statistical type II errors due to an insufficient sample size.

The risk of acquiring an invasive fungal infection (IFI) varies with the case mix of the study population. Allogeneic HSCT recipients with graft-versus-host disease or relapsed leukaemia patients are at higher risk than most other haematology patients; however, these high-risk, critically-ill subgroups were frequently under-represented or even excluded from prophylactic trials. Diluting the study population with patients at low risk (autologous transplants, short duration of neutropenia) favours demonstration of equivalence of two regimens. As a consequence, sample size, case mix and treatment imbalances impacted heavily on the strength of our recommendations (A–E).

A reduction of the number of proven and probable IFIs and an improvement in fungal-free survival and overall survival are the main objectives of PAC. Therefore, these end-points were given the highest priority. These end-points were however not always reported. Hence, surrogate end-points for efficacy were reported, including the impact on persistent fever, the frequency of possible IFIs, the use of empirical antifungal therapy and the mortality attributable to IFI. Although these latter end-points are poorly defined and usually highly subjective, mainly due to divergence in clinical management, we still tried to rate and to incorporate the impact of PAC on these different components before generating an overall recommendation. Toxicity and tolerability data, drug interaction profiles, patient's compliance and quality of life assessments, if available, were also included in the assessment of the strength of the recommendation (A–E).

According to the common methodology used in all working groups in preparation of the ECIL meeting, a list of priority questions were proposed by the organizing committee and redefined by the working group, including:

- Can we identify patient populations that are likely to benefit from PAC?
- Is PAC having an impact on the incidence of invasive fungal infections (yeast versus mould), on overall mortality, on fungal infection-related mortality, on the use of empirical antifungal therapy and on toxicity?
- Is PAC associated with increased resistance or selection of specific pathogens?
- How long should PAC be continued?
- Should serum levels of specific antifungal compounds be measured and what is the target level?

3. Results

3.1. *Questionnaire*

Eighty-seven percent of the 38 investigators answering the questionnaire gave antifungal prophylaxis: 85% gave prophylaxis to allogeneic HSCT, 63% to autologous HSCT and to AL patients. The distribution of antifungal agents is shown in Table 1. For allogeneic HSCT, the duration of prophylaxis was highly variable and ranged from including the neutropenic phase only (18%) to until day +100 (16%) or resolution of graft-versus-host disease (13%) or both (16%). The main reason for giving prophylaxis was to prevent superficial fungal infections (21%), yeast (25%) or mould (11%) infections specifically, invasive fungal infections in general (13%) and to reduce mortality (13%). Only 15 of the 38 investigators considered their attitude supported by the literature (see Table 2).

3.2. *Literature analysis*

Patients diagnosed with leukaemia represent a heterogenous population in terms of evolution of their underlying disease (acute versus chronic), intensity of therapy (intensive chemotherapy ± allogeneic transplantation versus a wait-and-see policy) and risk of developing opportunistic infections. Although future treatment options may render the so-called low-risk leukaemia patients (chronic leukaemia and low-risk MDS patients) more at risk for invasive fungal infections, the population that is nowadays most likely to benefit from antifungal prophylaxis consists of patients with an expected incidence of invasive fungal infections of at least 10%. This population includes acute leukaemia and high-risk MDS patients as well as patients undergoing haematopoietic stem cell transplantation (allogeneic > autologous). As such, our recommendations will only apply to these latter groups.

Table 1 – Results of the questionnaire (*N* = 38): distribution of antifungal agents used in prophylactic regimens according to the underlying condition

Agent (%)	Allogeneic HSCT	Autologous HSCT	Induction chemotherapy
Fluconazole	**57.1**	**57.1**	**55**
Itraconazole capsules	7.1	9.5	5
Itraconazole oral solution	**21.4**	**14.3**	**20**
Itraconazole intravenous	3.6	4.8	5
Voriconazole	3.6	4.8	5
Liposomal Ampho B	3.6	–	–
Nystatin	10.7	14.3	15
Non-absorbable Ampho B	**17.9**	**19.0**	**25**
Aerosolized Ampho B	7.1	–	–

Table 2 – Antifungal prophylaxis in leukaemia patients: ECIL recommendations

Allogeneic haematopoietic stem cell transplantation	
Fluconazole 400 mg qd intavenous (i.v.)/oral	AI
Itraconazole 200 mg IV followed by oral solution 200 mg bid	BI[b]
Posaconazole 200 mg tid oral	AI[c]
Micafungin 50 mg qd i.v.	CI
Polyene[a] i.v.	CI
Induction chemotherapy acute leukemia	
Fluconazole 50–400 mg qd i.v./oral	CI
Itraconazole oral solution 2.5 mg/kg bid	CI[b]
Posaconazole 200 mg tid oral	AI[c]
Candins i.v.	No data
Polyene[a] i.v.	CI–CII

a Includes low-doses of amphotericin B deoxycholate and lipid formulations of amphotericin B The ECIL recommendation for aerosolised amphotericin B deoxycholate is DI.
b May be limited by drug interactions and/or patient tolerability.
c Provisional recommendation (see text).

3.2.1. Azoles

– *Fluconazole:* Fluconazole is an attractive agent for antifungal prophylaxis because of its systemic effect, ease of administration and favourable safety profile. In the 1990s, the papers by Goodman and Slavin have set the trend for the widespread use of fluconazole prophylaxis.[7,8] Although a significant reduction of the incidence of IFI and of the overall mortality has only been shown for patients undergoing HSCT, fluconazole prophylaxis has also become the standard of care in patients undergoing intensive chemotherapy for AL and MDS.[9–12] In a meta-analysis by Bow et al., fluconazole prophylaxis reduced the use of parenteral antifungal therapy (including the empirical use), the incidence of superficial fungal infections and of invasive *Candida* infections, and the fungal infection-related mortality.[13] In addition, fluconazole prophylaxis decreased the overall mortality, but only in the subset of patients with prolonged neutropenia and in those undergoing HSCT.[13,14] A daily dose of 400 mg is recommended. Subsequent studies have suggested but not proven that lower daily doses of fluconazole (50–200 mg) may suffice for fungal prevention during induction chemotherapy.[12] Of note, fluconazole is ineffective against moulds and *Candida krusei* and displays a dose-dependent activity against some strains of *C. glabrata*. This spectral shortcoming results in the occurrence of breakthrough infections.
ECIL recommendation:
  - allogeneic HSCT: fluconazole 400 mg/day: AI;
  - autologous HSCT or acute leukaemia: fluconazole 50–400 mg/day: CI.
– *Itraconazole:*
  - *Capsules*: Itraconazole displays a broad spectrum of activity, including *Aspergillus* species. In randomised trials using the capsule formulation (200–400 mg/day), the incidence of IFIs was not significantly different from the respective comparator drugs (fluconazole 100 mg/d; placebo ± oral amphotericin B).[15–17]
  - *Oral solution*: The increased bioavailability of the oral solution formulation has been demonstrated in autologous HSCT recipients and in patients with AL. Data on the prophylactic efficacy of this formulation in haematology patients are available from five prospective, randomised multicentre trials.[18–22] However, no single study has convincingly demonstrated a reduction in the number of *Aspergillus* infections or an improvement in the overall or fungal-free survival. Lack of superiority may result from flaws in trial methodology and patient recruitment, including the use of a non-blinded design,[19] the exclusion of allogeneic HSCT recipients and the absence of regimens that are more frequently associated with IFIs (e.g. high-dose cytarabine, with or without fludarabine).[18] According to a recent meta-analysis however, itraconazole oral solution (at least 400 mg/day) effectively prevents proven invasive fungal infections (including invasive aspergillosis) and reduces mortality from these infections.[23]
  - *Intravenous followed by oral solution*: The prolonged use of adequately dosed itraconazole (200 mg intravenous (i.v.) followed by the oral solution 200 mg bid) versus fluconazole (400 mg oral or i.v.) has been evaluated in two open-label studies in myeloablative allogeneic HSCT recipients.[24,25] Both the studies have demonstrated a higher efficacy of itraconazole in preventing invasive mould infections. However, the study of Winston et al. was hampered by imbalances in patients characteristics in favour of itraconazole,[24] whereas that of Marr et al. (using a high-dose of 2.5 mg/kg tid) showed a 36% dropout rate in the itraconazole arm due to intolerance and toxicity.[25] This latter observation is consistent with the findings of a recent meta-analysis.[26] In addition, Marr reported unexpected liver toxicity when itraconazole was used concomitantly with cyclophosphamide.[27] So, the potential for hazardous drug interactions represents another drawback.
  ECIL recommendation:
    - in allogeneic HSCT: itraconazole 200 mg/day IV followed by oral solution: BI;
    - in autologous HSCT and acute leukaemia: *itraconazole oral solution 2.5 mg/kg bid: CI;*
    - itraconazole capsules: EI.
  - *Should itraconazole levels be measured?* Given the marked variations in bioavailability and the significant dose–response relationship, therapeutic drug monitoring is recommended to ensure adequate plasma levels (a thorough concentration of at least 500 ng ml^{-1} itraconazole measured by high-performance liquid chromatography) at steady state (*ECIL recommendation BII*).[28]

3.2.2. Aerosolized amphotericin B (AMB) deoxycholate

Contrary to yeast infections, mould infections are primarily airborne. Thus, delivering high concentrations of AMB to the airways by aerosolising the drug represents an appealing approach. Unfortunately, the only randomised study in this field found no difference in the incidence of invasive pulmonary aspergillosis or in overall mortality between patients who

received inhalations and those who did not. Moreover, intolerance led to the premature discontinuation in ~30% of cases.[29] It remains to be seen whether the use of a lipid formulation of AmB or a powder formulation will increase efficacy and tolerance.

ECIL recommendation: DI.

3.2.3. *Systemic low-dose AMB deoxycholate*

Some investigators have examined the use of low-doses of intravenous AMB (ranging from 0.5 mg/kg/day to <0.1 mg/kg/day), with or without intranasal sprays. In retrospective analysis, this approach decreased both the incidence of invasive aspergillosis and the transplant-related mortality in allogeneic HSCT recipients. However, these results are inconclusive due to the use of historical controls and due to the presence of confounding environmental and prognostic factors.[30,31]

ECIL recommendation: CII.

3.2.4. *Lipid formulations of AMB*

Two placebo-controlled, double-blind randomised studies (using liposomal AMB 1 mg/kg/day or 2 mg/kg three times weekly) have been performed in HSCT recipients and in patients receiving chemotherapy.[32,33] However, these studies were not sufficiently powered to detect a superiority of liposomal AMB over placebo. Thus, although associated with an encouraging trend towards a reduced incidence of IFI, the difference could not reach statistical significance. Unexpectedly, no single case of proven invasive aspergillosis was observed in these series, not even in the control group. A randomised trial comparing fluconazole versus ABCD was terminated prematurely because of severe infusion-related side effects in the ABCD-arm.[34]

ECIL recommendation: CI.

3.2.5. *Echinocandins*

The echinocandins display activity against *Candida* and *Aspergillus* species. These agents induce little toxicity and are not metabolised through the cytochrome P450 enzymes. Therefore, echinocandins represent a safe alternative to fluconazole and yield activity against invasive aspergillosis. The prophylactic efficacy of micafungin (50 mg) was compared with fluconazole (400 mg) in a double-blind, multicenter study during the neutropenic phase of HSCT.[35] The study concluded that the overall efficacy of micafungin was superior to that of fluconazole (including decreased use of empirical antifungal therapy but no difference in overall mortality). Unfortunately, this study included a large number (70%) of autologous and low-risk allogeneic transplants and did not address the prevention of late IFIs.

ECIL recommendation:

- in HSCT: micafungin 50 mg: CI;
- in acute leukemia: no data;
- caspofungin or anidulafungin: no data.

3.2.6. *Posaconazole*

Following the consensus approval of the first ECIL recommendations on antifungal prophylaxis on October 1st, 2005, results from two additional large (~600 enrolled patients), randomised prophylactic trials have become available. The first study was an open-label but evaluator-blinded study that compared posaconazole oral suspension (200 mg tid) versus standard azole prophylaxis (itraconazole oral suspension 200 mg bid or fluconazole oral solution 400 mg qd) during remission-induction chemotherapy of patients with AML/MDS. The study showed a significant reduction in the number of proven and probable invasive fungal infections (including a significant reduction in the number of *Aspergillus* cases) and demonstrated a statistically significant benefit in overall survival and fungal-free survival in favour of posaconazole.[36] The second study, a double-blind, double-dummy study compared posaconazole oral solution (200 mg tid) versus fluconazole capsules 400 mg qd in allogeneic stem cell transplant recipients with acute or chronic graft-versus-host disease necessitating severe immunosuppressive therapy. In this study posaconazole proved to be non-inferior to fluconazole during the fixed time period of 112 days that was used for the primary end-point analysis. In addition, posaconazole resulted in a significant reduction of the number of proven and probable invasive fungal infections (including *Aspergillus* infections) while on treatment. No survival benefit was seen in this study.[37]

Given the importance of these results but pending the full publication of these studies as well as the in-depth discussion within the next plenary ECIL meeting in 2007, the members of the Working Party and the Chairmen of the prophylaxis session decided to include a *provisional* AI recommendation for posaconazole prophylaxis (200 mg tid) during induction chemotherapy for AML/MDS and during intensive immunosuppressive therapy for acute and chronic GvHD following allogeneic haematopoietic stem cell transplantation.

3.2.7. *Antifungal prophylaxis and changes in fungal epidemiology*

Several reports have pointed out that the use of antifungal prophylaxis has the potential for induction of resistance and results in the selection of natively resistant organisms, potentially leading to a change in the epidemiology of fungal infections. For instance, the use of fluconazole prophylaxis resulted in a ~8-fold increase in the frequency of *Candida glabrata* colonisation and resulted in a shift towards non-albicans *Candida* infections in allogeneic transplant recipients.[35,38] Also, pre-exposure of cancer patients to amphotericin B or triazoles was associated with increased frequency of non-fumigatus *Aspergillus* species. These *Aspergillus* isolates exhibited higher E-test amphotericin B MICs compared with isolates from patients without prior antifungal exposure.[39] Hence, we feel that patients who receive prolonged antifungal prophylaxis should be closely monitored for changes in the colonising fungal flora and in the causative fungal pathogens.

3.2.8. *Duration of antifungal prophylaxis*

In the absence of trials, no firm recommendation regarding the optimal duration of antifungal prophylaxis can be given. However, in neutropenic patients, most experts would agree to continue prophylaxis until recovery of the neutrophil count (ANC > 500/μL) (BIII). In allogeneic transplant recipients, antifungal prophylaxis should probably be continued till day +75

posttransplant (14) or till the end of immunosuppression,[40] whichever comes first (BIII).

4. Conclusion and future prospects

The efficacy of PAC should be assessed in randomised trials, based on an adequate sample size with sufficient statistical power to detect differences between both study arms. These trials should implement uniform and universally accepted criteria of case-definitions and outcome-analysis (incidence of proven candidiasis, incidence of proven and probable aspergillosis, overall mortality and fungal-free survival) and should target high-risk patients only. These objectives can only be achieved by multi-institutional collaboration. Many of the shortcomings in the design of previous studies are or have been addressed in ongoing (e.g. voriconazole versus fluconazole in allogeneic HSCT recipients) or recently closed multicentre studies. Finally, the issue of secondary antifungal prophylaxis (in patients with a previous episode of IFI who are scheduled for a subsequent immunosuppressive or cytotoxic therapy) should also be addressed in prospective clinical trials.

Conflict of interest statement

J.M. has received funds for speaking at symposia organised on behalf of Pfizer, MSD, Schering-plough, Zeneus, and Gilead Science. J.M. is a member of the MSD, Schering-Plough, Zeneus, and Gilead advisory boards for antifungal agents.

O.A.C. has received research grants from Astellas, Basilea, Gilead, Pfizer, Merck, Schering-Plough, and Vicuron, is a consultant to Astellas, Basilea, Gilead, Pfizer, Merck, Nektar, Schering-Plough, and Zeneus, and served at the speakers bureau of Astellas, Gilead, Merck, and Schering-Plough.

P.F., C.L., and W.H.: nothing to declare.

Acknowledgements

Reviewed by Winfried Kern, Department of Medicine, University Hospital, Freiburg, Germany, and Chris Kibbler, Royal Free Hospital, London, UK.

REFERENCES

1. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of cancer (EORTC). *Clin Infect Dis* 1999;**28**:1071–9.
2. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001;**32**:358–66.
3. von Eiff M, Roos N, Schulten R, et al. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration* 1995;**62**:341–7.
4. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. *Lancet Infect Dis* 2005;**5**:609–22.
5. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001;**33**:139–44.
6. de Pauw B. Preventative use of antifungal drugs in patients treated for cancer. *J Antimicrob Chemother* 2004;**53**:130–2.
7. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *New Engl J Med* 1992;**326**:845–51.
8. Slavin MA, Osborne B, Adams R, 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.
9. Rotstein C, Bow EJ, Laverdiere M, et al. Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. *Clin Infect Dis* 1999;**28**:331–40.
10. Schaffner A, Schaffner M. Effect of prophylactic fluconazole on the frequency of fungal infections, amphotericin B use, and health care cost in patients undergoing intensive chemotherapy for hematological neoplasias. *J Infect Dis* 1995;**172**:1035–41.
11. Winston DJ, Chandrasekar PH, Lazarus HM, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized, placebo-controlled, double-blind, multicenter trial. *Ann Intern Med* 1993;**118**:495–503.
12. Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with haematological malignancies. *Blood* 2003;**101**:3365–72.
13. Bow EJ, Laverdiere M, Lussier N, et al. Antifungal prophylaxis for severely neutropenic chemotherapy patients. A meta-analysis of randomized-controlled clinical trials. *Cancer* 2002;**94**:3230–46.
14. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood* 2000;**96**:2055–61.
15. Huijgens PC, Simoons-Smit AM, Van Loenen AC, et al. Fluconazole versus itraconazole for the prevention of fungal infections in haemato-oncology. *J Clin Pathol* 1999;**52**:376–80.
16. Nucci M, Biasoli I, Akiti T, et al. A double-blind, randomized, placebo-controlled trial of itraconazole capsules as antifungal prophylaxis for neutropenic patients. *Clin Infect Dis* 2000;**30**:300–5.
17. Vreugdenhil G, Van Dijke BJ, Donnelly JP, et al. Efficacy of itraconazole in the prevention of fungal infections among neutropenic patients with hematological malignancies and intensive chemotherapy. A double blind, placebo controlled study. *Leuk Lymph* 1993;**11**:353–8.
18. Menichetti F, Del Favero A, Martino P, et al. Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomized, placebo-controlled, double-blind, multicenter trial. *Clin Infect Dis* 1999;**28**:250–5.
19. Morgenstern GR, Prentice AG, Prentice HG, et al. A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. *Br J Haematol* 1999;**105**:901–11.
20. Harousseau J-L, Dekker AW, Stamatoullas-Bastard A, et al. Itraconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo multicenter trial comparing itraconazole and amphotericin B. *Antimicrob Agents Chemother* 2000;**44**:1887–93.
21. Boogaerts M, Maertens J, Van Hoof A, et al. Itraconazole versus amphotericin B plus nystatin in the prophylaxis of fungal infections in neutropenic cancer patients. *J Antimicrob Chemother* 2001;**48**:97–103.

22. Glasmacher A, Cornely O, Ullmann AJ, et al. An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. *J Antimicrob Chemother* 2006;**57**:317–25.
23. Glasmacher A, Prentice A, Gorschluter M, 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.
24. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomised trial. *Ann Intern Med* 2003;**138**:705–13.
25. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood* 2004;**103**:1527–33.
26. Vardakas KZ, Michalopoulos A, Falagas ME. Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. *Br J Haematol* 2005;**131**:22–8.
27. Marr KA, Crippa F, Leisenring W, et al. Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004;**103**:1557–9.
28. Glasmacher A, Hahn C, Molitor E, et al. Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-β-cyclodextrin oral solution or coated-pellet capsules. *Mycoses* 1999;**42**:591–600.
29. Schwartz S, Behre G, Heinemann V, et al. Aerosolized amphotericin B inhalations as prophylaxis of invasive Aspergillus infections during prolonged neutropenia: results of a prospective, randomized trial. *Blood* 1999;**93**:3654–61.
30. Rousey SR, Russler S, Gottlieb M, et al. Low-dose amphotericin B prophylaxis against invasive *Aspergillus* infections in allogeneic marrow transplantation. *Am J Med* 1991;**91**:484–92.
31. Perfect JR, Klotman ME, Gilbert CC, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. *J Infect Dis* 1992;**165**:891–7.
32. Tollemar J, Ringdén O, Andersson S, et al. 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.
33. Kelsey SM, Goldman JM, McCann S, et al. Liposomal amphotericin B (Ambisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study. *Bone Marrow Transplant* 1999;**23**:163–8.
34. Timmers GJ, Zweegman S, Simoons-Smit AM, et al. Amphotericin B colloidal dispersion (Amphocil) vs. fluconazole for the prevention of fungal infections in neutropenic patients: data of a prematurely stopped clinical trial. *Bone Marrow Transplant* 2000;**25**: 879–84.
35. van Burik JA, Ratanatharathorn V, Stepan DE, 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.
36. Cornely O, Maertens J, Winston D, et al. Posaconazole versus standard azole therapy for prophylaxis of invasive fungal infections among high-risk neutropenic patients: results of a randomized, multicenter trial. In: Abstracts of the 47th annual meeting of the American society of hematology, Atlanta, Georgia; 2005 [abstract 48-II].
37. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole versus fluconazole for prophylaxis of invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease: results of a multicenter trial. In: Abstracts of the 45th Interscience Conference on antimicrobial Agents and Chemotherapy, Washington, DC. American Society for Microbiology, Washington (DC, USA); 2005. p. 418 [abstract M-716].
38. Marr KA, Seidel K, White TC, et al. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. *J Infect Dis* 2000;**181**:309–16.
39. Lionakis MS, Lewis RE, Torres HA, et al. Increased frequency of non-fumigatus *Aspergillus* species in amphotericin B- or triazole-pre-exposed cancer patients with positive cultures for aspergilli. *Diagn Microbiol Infect Dis* 2005;**52**:15–20.
40. Trifilio S, Verma A, Mehta J. Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: heterogeneity of current clinical practice. *Bone Marrow Transplant* 2004;**33**:735–9.