REVIEW 10.1111/j.1469-0691.2012.03772.x

Antifungal prophylaxis in haematology patients: the role of voriconazole

Y. Hicheri[1], G. Cook[2] and C. Cordonnier[1]

1) Service d'Hématologie Clinique, Assistance Publique-Hopitaux de Paris, Hôpital Henri Mondor, University Paris Est-Créteil, Créteil, France and 2) Department of Haematology, St James's Institute of Oncology, Leeds Teaching Hospitals, Leeds, UK

Abstract

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in haematopoietic stem cell transplant (HCT) recipients and patients with haematological malignancies. Early treatment initiation is vital for improving survival, but is hampered by difficulties in timely diagnosis. Prophylaxis with a broad-spectrum antifungal, such as voriconazole, has the potential to decrease the incidence of IFI in haematology patients. Based on a growing body of data, voriconazole appears to be effective for the primary and secondary prevention of IFIs in HCT recipients, with generally good tolerability.

Keywords: Antifungal prophylaxis, haematology, leukaemia, stem cell transplantation, voriconazole

Clin Microbiol Infect 2012; **18** (Suppl.2): 1–15

Corresponding author: C. Cordonnier, Service d'Hématologie Clinique, Assistance Publique-Hopitaux de Paris, Hôpital Henri Mondor, University Paris Est-Créteil, 51, Av. Maréchal de Lattre de Tassigny, 94000 Créteil, France
E-mail: carlcord@club-internet.fr

Introduction

Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality in haematology patients. Haematopoietic stem cell transplant (HCT) recipients and patients with haematological malignancies are particularly vulnerable, as a consequence of their underlying condition, its treatment, or prolonged immunosuppression [1–6]. Invasive aspergillosis (IA) is the most important IFI in these populations and is the leading cause of infection-related death in HCT recipients [7]. The onset of invasive *Aspergillus* infection following HCT appears to be bimodal, occurring more frequently during the graft-versus-host disease (GvHD) period late after engraftment [3,8,9]. Patients undergoing autologous HCT rarely present with IA and have a distinctly lower attributable mortality rate than allograft recipients [10]. Besides IA, other invasive mould infections and invasive candidiasis are also fairly common [3,6,8,11,12]. Recent data show that about three-quarters of IFIs in HCT patients are caused by moulds, mostly in the form of IA (59–71%), with the remainder caused by *Candida* spp. [10,13,14]. Furthermore, invasive mould infections, especially those caused by *Aspergillus*, appear to be becoming increasingly frequent in various haematology populations [3,4,8].

These trends are probably linked to the growing number of at-risk patients (e.g. elderly patients undergoing reduced-intensity conditioning HCT, solid organ transplant recipients, and critically ill patients) as well as the increasing prevalence of risk factors rendering patients susceptible to IFIs in general and invasive mould infections in particular. Such risk factors include cytotoxic chemotherapy, neutropenia, GvHD, immunosuppressant therapy, broad-spectrum antibiotics, use of intravenous catheters, parenteral nutrition and renal failure [1,3]. In haematology patients, the risk for developing an IFI depends strongly on the severity and duration of myelosuppression and immunosuppression [15]. The overall developments in epidemiology are of concern because IFIs are associated with substantial mortality. In Europe, mortality rates range from 27 to 94% for IA and from 28 to 59% for invasive candidiasis [10,16–24].

Although early initiation of therapy is vital for improving treatment outcomes, the timely diagnosis and treatment of IFIs pose considerable challenges [3,25,26]. Given the lack of validated early treatment strategies, mould-active prophylaxis

may currently be the most attractive option for the management of IFIs in specific groups of haematology patients, until tests for the early detection of IFI have become more reliable [26–30]. This preventative approach has the potential of decreasing IFI incidence and concurrently improving survival in haematology patients; however, data from recent clinical trials suggest that it does not entirely avoid the need for additional empirical or pre-emptive therapy [31–34].

There are also some concerns about the widespread application of antifungal prophylaxis, such as induction of antimicrobial resistance, shifts in epidemiology, avoidable drug toxicity and costs, and considerable variability in the plasma levels of certain antifungals [15,27,35]. This review will address current issues in antifungal prophylaxis for HCT recipients and haematological malignancy patients, with a particular focus on recent data supporting the potential value of voriconazole in this setting.

Antifungal prophylaxis

The use of any chemoprophylaxis in medicine ought to be supported by a number of key tenets. For instance, the disease to be prevented should be associated with a high mortality rate, and the preventative agent should have an acceptable efficacy and safety profile. Furthermore, optimum IFI prophylaxis requires the selection of patients at highest risk of invasive fungal disease, to limit drug exposure to those individuals who are most likely to benefit from this strategy [36,37]. Novel approaches toward the identification of high-risk patients have shown the importance of host innate immunity, with several genetic polymorphisms (i.e. of *TLR4*, *IL10*, *DECTIN*-1, and the plasminogen gene) having potential as specific risk markers [35,38]. Some authors propose to restrict prophylaxis with broad-spectrum azoles to those institutions that have a relatively high incidence of invasive mould infections or that do not routinely employ effective strategies for early diagnosis and treatment [36,39]. However, so far there is no consensus on how to define populations of haematology patients that are at 'high-risk for IFI' on the basis of a minimum IFI incidence rate or a minimum number needed-to-treat, and in whom primary antifungal prophylaxis may therefore be preferable to other management approaches. Besides chemoprophylaxis, protective isolation in conjunction with the use of high-efficiency particulate air filtration systems may also be useful for the prevention of systemic mould infections in patients undergoing allogeneic HCT or chemotherapy for acute leukaemia [1,36].

The optimal duration of antifungal prophylaxis in haematology patients also remains to be confirmed. In HCT recipients, prophylactic therapy may need to be administered for a minimum of 6 months following transplant [15], in particular when considering the increasing frequency of late-onset IA [8,26]. The efficacy of antifungal prophylaxis during this time may partially depend on the degree of immunosuppression, as indicated by biological markers (e.g. levels of CD4 T lymphocytes) [15]. Also still unknown are the most effective agents for antifungal prophylaxis in HCT recipients or patients receiving chemotherapy for haematological disease (Table 1) [31,32,34,40–48], even though mould-active azoles seem to have the most potential in these settings. Among that class of agents, the second-generation, broad-spectrum triazole voriconazole is emerging as a new option for primary and secondary antifungal prophylaxis.

The potential of voriconazole as antifungal prophylaxis

Voriconazole is currently indicated for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, and serious infections caused by *Scedosporium* and *Fusarium* spp. Furthermore, in Europe the agent is licensed for the treatment of fluconazole-resistant serious invasive *Candida* infections and in the USA for oesophageal candidiasis and disseminated *Candida* infections in skin, abdomen, kidney, bladder wall and wounds [49,50]. This variety of indications is reflected by the broad *in vitro* spectrum of voriconazole against yeasts and moulds, including *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Scedosporium apiospermum*, dematiaceous moulds, *Cryptococcus neoformans* and dimorphic fungi. Of note, voriconazole is not active against the zygomycetes and may have reduced activity against certain strains of *Candida glabrata* and *Candida albicans* that have acquired fluconazole resistance [51].

The extended spectrum of voriconazole gives it potential value as a prophylactic agent. The *in vitro* coverage and documented clinical efficacy of voriconazole against the majority of fungal pathogens [20,51–55] may make it particularly useful for the prevention of IFIs in the haematology setting, where invasive mould infections play a prominent role. Of note, voriconazole is now generally recommended as first-line treatment for proven or probable IA [56–60], the most significant systemic fungal disease affecting haematology populations; a recent mixed-treatment comparison suggested that voriconazole may be the most effective antifungal for improving patient survival in the setting of directed therapy [61]. On the other hand, the very fact that voriconazole is widely considered the standard treatment for documented IA may pose an issue when using mould-active azoles prophylactically in the same patient population, because of the risk of selection