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The role of primary antifungal prophylaxis in patients with haematological malignancies

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Abstract

Invasive fungal infections (IFIs) represent important complications in patients with haematological malignancies. Chemoprevention of IFIs may play an important role in this setting, but in the past decades the majority of antifungal drugs utilized demonstrated poor efficacy, particularly in the prevention of invasive aspergillosis. The new triazoles are very useful antifungal drugs, more suitable for prophylaxis of IFIs than amphotericin B and echinocandins. In this review, the main clinical data about antifungal prophylaxis with fluconazole, itraconazole, voriconazole and posaconazole are analysed. At present, posaconazole appears to be the most efficacious azole in antifungal prophylaxis, particularly in patients with acute myeloid leukaemia.

Keywords: antifungal prophylaxis, fluconazole, itraconazole, leukaemia, posaconazole, stem cell transplantation, voriconazole
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Epidemiology of Fungal Infections in Haematology

Invasive fungal infections (IFIs) are a leading infectious cause of morbidity and mortality in patients with haematological malignancies [1]. Patients with haematological malignancies such as acute leukaemia, myelodysplastic syndromes and those undergoing allogenic haemopoietic stem cell transplant (allo-HSCT) are at major risk of IFIs [2]. In particular, the incidence of IFIs is higher in acute myeloid leukaemia (AML) [3]. In the recent past, some studies evaluated the incidence and outcome of IFIs in haematological malignancies. A retrospective study, conducted in a population of 11 802 haematological malignancies treated with conventional chemotherapy, showed an overall incidence of 4.6% proven/probable IFIs, but the incidence of IFIs was highest among patients with AML (*c.* 8%). In some settings, IFIs caused by moulds are more frequent than those caused by yeasts, and *Aspergillus* spp is the most common pathogen [4]. The risk of invasive aspergillosis (IA) is not constant over all the phases of AML treatment: the majority of AML patients usually experience IA after the first cycle of chemotherapy (1st induction), the first time that a colonized patient experiences deep immunosuppression. An IFI during the first induction may dramatically compromise the following therapeutical strategy for AML [5].

For this reason, antifungal prophylaxis of IFIs may have an important role in this setting; in the past decades, chemoprophylaxis with oral polyenes and old triazoles showed poor efficacy. At present, the availability of new triazoles (i.e. voriconazole, posaconazole) characterized by a wider spectrum may have modified the role of antifungal prophylaxis. In this review, the efficacy of the different antifungal prophylaxis used over the years will be analysed.

Past Role of Chemoprophylaxis

Several review articles evaluated the role of the prophylaxis of IFIs in the pre-new antifungals era [6–10]. Topical therapy with

oral polyenes has the potential to prevent candidiasis with less risk of side effects and drug interactions than systemic therapy. It has been found useful in prevention of serious *Candida* infection in high-risk patients [9,10]. However, this kind of prophylaxis has been disappointing, particularly against *Aspergillus*.

Some years ago, Uzun and Anaissie described some criteria to identify the optimal antifungal agent. The ideal prophylactic agent should be safely administrable over long periods, effective, fungicidal against a wide spectrum of fungal pathogens, inexpensive, available in both oral and intravenous formulation and associated with a low incidence of resistance [11]. These criteria identified triazoles as a very useful class of oral antifungal drugs, more suitable for chemoprophylaxis of IFIs than AmB and other drugs, available only in intravenous (iv) formulation.

Fluconazole

Fluconazole was the first azole systematically used for chemoprophylaxis of IFIs. Due to its high systemic activity and low toxicity, fluconazole facilitated an earlier and prophylactic use of systemic antifungals, and it is not contraindicated in patients receiving cyclosporine prophylaxis against graft-versus-host disease (GVHD). However, it appears effective only in high doses, commonly associated with adverse reactions [6–8]. Fluconazole is active against the most of *Candida* strains, although some strains are inherently resistant (i.e. *Candida kruzei or Candida glabrata*) [12].

Randomized, double-blind, placebo-controlled trials evaluated fluconazole as antifungal prophylaxis for HSCT recipients. Goodman *et al.* studied 356 autologous and allo-HSCT recipients from multiple centres, using fluconazole (400 mg/day) or placebo from the start of the conditioning period for a maximum of 10 weeks. IFIs occurred in 28 patients who received placebo as compared with five who received fluconazole (15.8% vs. 2.8%, $p < 0.001$). Fluconazole prevented infection with all species of *Candida* except *C. krusei*. Fewer infection-related deaths occurred in the fluconazole arm of the study (1/179 vs. 10/177, $p < 0.001$), but fluconazole did not significantly alter overall mortality [13]. In a second study, Slavin and coworkers sought to determine whether a longer course of prophylaxis with fluconazole would improve survival or lower the incidence of infections. They administered fluconazole (400 mg/day for 75 days) to allo-HSCTs. The rate of IFIs in the fluconazole arm during prophylaxis was 10/152 patients (7%) vs. 26/148 patients (18%) in the placebo arm (p 0.004). The rate of IFI-related deaths by day 110 after transplant was 13% in the fluconazole arm and 21% in the placebo arm (p 0.005). In contrast to the Goodman study, at day 110, the probability of overall survival was improved among fluconazole recipients (20% vs. 35%, $p = 0.004$) [14]. However, it is noteworthy that at time of these studies, *Candida* spp. caused the majority of IFI, and this may explain fluconazole's good performance.

A post-mortem study carried out on 720 patients given fluconazole prophylaxis showed that they died of *Candida* infection less frequently than of *Aspergillus* IFI; however, it must be taken in account that the sensitivity of blood cultures decreased when patients received fluconazole prophylaxis, a possible evaluation bias. [15]. Several authors demonstrated that the intensive use of fluconazole prophylaxis in haematological malignancies selected multiresistant and difficult-to-treat species of *Candida* non-*albicans* [4,16–19]. Recent nationwide data in Denmark reported an increasing incidence of candidemia associated with a decreasing proportion being susceptible to fluconazole. The fluconazole MICs for *C. glabrata* and *C. krusei* were in general elevated compared with those for *C. albicans*; for *C. glabrata* in particular, the MIC distribution suggests acquired resistance mechanisms for a proportion of isolates [20].

Itraconazole

In contrast to fluconazole, itraconazole is active against *Aspergillus* spp; two studies compared the prophylactic activity of these two drugs in haematological patients undergoing allo-HSCT. In the first study, itraconazole in oral solution form was administered, and a significant reduction in IFIs incidence with itraconazole without differences in fungal-free survival was observed [21]. In a second study, itraconazole was administered initially intravenously and then as oral solution, and resulted in fewer proven IFIs and lower fungal-related mortality, but similar overall mortality, compared to fluconazole after allo-HSCT [22]. In both studies, mild gastrointestinal side effects in itraconazole arm were observed.

The study of the GIMEMA-infection group (Gruppo Italiano Malattie Ematologiche dell'Adulto) that compared itraconazole oral solution to placebo, did not show advantage to itraconazole regarding the incidence of invasive aspergillosis, but a significant reduction in candidemia was observed [23].

However, an interesting meta-analysis evaluated the efficacy of itraconazole vs. other forms of prophylaxis for the prevention of IFIs in neutropenic cancer patients after chemotherapy or allo-HSCT. The meta-analysis of 13 randomized trials in 3597 neutropenic patients with haematological malignancies showed a significant reduction in the incidence of IFIs (p 0.002), of invasive yeast infections (p 0.004) and mortality from IFIs (p 0.04), with a highly significant dose–response relationship [24].