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Prophylaxis of invasive fungal diseases in patients with hematologic disorders

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Invasive fungal diseases are associated with significant morbidity and mortality among neutropenic patients after chemotherapy and in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Considering that it is difficult to make an early diagnosis, the prophylaxis of these complications is appealing. Prevention strategies are based on environmental precautions and antimicrobial agents. While there is a general agreement on the role of air filtration in the control of airborne filamentous fungal infections, the indication for pharmacological prophylaxis is still debated.[1]

Until a few years ago, only fluconazole and itraconazole had been evaluated in randomized, controlled trials for primary antifungal prophylaxis in patients with hematologic disorders.[2-4] In view of the results of these studies, international guidelines did not recommend primary antifungal prophylaxis for all neutropenic patients, including those who had undergone autologous HSCT or had acute leukemia, and only recommended prophylaxis of *Candida* infections with oral or intravenous fluconazole for allogeneic HSCT recipients during the period of neutropenia until engraftment.[5-7]

In recent years, awareness of the epidemiological impact of invasive aspergillosis and less common molds, including zygomycetes, *Fusarium* species and *Scedosporium* species, has increased worldwide. At the same time, new broad spectrum and well tolerated antifungal drugs, in particular second generation triazoles (posaconazole and voriconazole) and echinocandins, became available, and prospective, controlled trials have been conducted to investigate their ability to prevent invasive fungal infections in high-risk hematologic patients.[8-10] Based on the above studies, current international guidelines continue to recommend the use of fluconazole until engraftment in patients who have undergone allogeneic HSCT, and, for the first time, recommend the use of a broad spectrum drug, oral posaconazole, during intensive immunosuppressive therapy for graft-*versus*-host disease, and in patients with acute myeloid leukemia or myelodysplastic syndromes during remission induction chemotherapy.[11-13] These recommendations reflect important progresses obtained in the prevention of invasive fungal infections, including those caused by filamentous fungi, but they have been unable to generate a consensus on the optimal prophylaxis of invasive fungal infections in the complex scenario of hematologic disorders, particularly in the transplant setting. This problem has been underlined in a recent consensus process by the *Gruppo Italiano Trapianto di Midollo Osseo* (GITMO) which observed that key recommendations by international guidelines imply various problems such as the lack of any approved mold-active prophylaxis during the engraftment phase in allogeneic HSCT, and the lack of an intravenous formulation of posaconazole, which could limit the use of this drug in patients unable to tolerate oral medications or with altered intestinal absorption.[14] Based on the preliminary results of two controlled studies of primary prophylaxis with voriconazole in allogeneic HSCT recipients during engraftment and graft-*versus*-host disease phases, and pending publication as full papers, the 2009 updated European guidelines (ECIL 3) provisionally recommended the use of voriconazole in both phases of HSCT.[13]

An evidence-based approach to secondary antifungal prophylaxis in patients with a previous invasive fungal infection who require further antileukemic treatment remains even more challenging. An anti-infection strategy

in the setting of leukemia and transplantation can be considered clinically effective when the control of the infection enables optimal cure of the underlying hematologic disease. Thanks to the use of antifungal drugs in secondary prophylaxis, an invasive fungal infection, including invasive aspergillosis, is no longer an absolute contraindication to continuing care with intensive chemotherapy or HSCT. However, very few data exist on factors that could predict reactivation of invasive fungal disease during secondary prophylaxis, on the choice of the best antifungal drug or on the need for preventive surgical resection of residual pulmonary lesions. Only retrospective studies on secondary antifungal prophylaxis in patients with heterogeneous baseline characteristics and undefined risk of reactivation have been published so far.[15-17] The largest series reported up to now was a group of 129 patients in a retrospective survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT): these were patients who had a previous history of probable or proven invasive aspergillosis who underwent allogeneic HSCT.[17] The cumulative incidence of progression of invasive aspergillosis 2 years after transplantation was 22% and it was found that duration of post-transplantation neutropenia, status of the underlying disease, and duration of pre-transplantation anti-*Aspergillus* therapy were factors determining the progression or reactivation of invasive aspergillosis while under secondary prophylaxis.

In this issue of the journal, Cordonnier *et al.* report on a prospective, non-comparative, multicenter study of 45 patients who received voriconazole as secondary prophylaxis of invasive fungal infections for a median duration of 94 days after allogeneic HSCT.[18] The 1-year cumulative incidence of invasive fungal infection was 6.7±3.6%. Two relapses of infection (one candidemia and one fatal scedosporiosis) and one new breakthrough zygomycosis in a patient with a previous invasive aspergillosis occurred post-transplantation. None of the 31 patients with a previous proven or probable invasive aspergillosis experienced recurrence of their infection. Voriconazole was discontinued in only two patients because of treatment-related hepatotoxicity. This is the first prospective evidence of the efficacy and safety of secondary antifungal prophylaxis in protecting allogeneic HSCT recipients from recurring invasive fungal infection. However, considering that most of patients in this series were in complete clinical and radiological remission of their invasive fungal infection, with a presumably low risk of reactivation, this study does not seem to clarify the role of secondary prophylaxis with voriconazole in the control of a residual or active invasive fungal disease at high risk of reactivation during the post-transplantation period when patients are immunocompromised.

Several open issues in the prophylaxis of invasive fungal infections in patients with hematologic disorders deserve careful consideration: i) primary antifungal prophylaxis may be indicated in acute leukemia settings other than acute myeloid leukemia after remission-induction chemotherapy, such as during consolidation chemotherapy for acute myeloid leukemia or in adult patients with acute lymphoid leukemia being treated with acute myeloid leukemia-like chemotherapy schedules. The local epidemiology of fungal infections probably represents a criterion for the choice to extend the indications of primary antifungal prophylaxis in leukemia patients; ii) in allogeneic HSCT recipients, mold-active primary antifungal prophylaxis may be indicated in risk settings other than graft-*versus*-host disease. Transplant procedures with alternative stem cell sources, such as cord blood or haploidentical donors in adult patients, are being increasing used and are associated with a high risk of infections; aggressive and prolonged prophylaxis strategies during and after the engraftment phase may be indicated in these cases;[13,14,19,20] iii) Secondary antifungal prophylaxis is widely used in clinical practice but there is no consensus regarding the indications, the duration of treatment and the drug of choice. While several studies, including that by Cordonnier *et al.*, seem to show that suppressive antifungal therapy in patients with infection in microbiological, clinical and radiological remission prevents reactivation of the disease despite prolonged neutropenia or profound immunosuppression post-allografting, the efficacy of secondary antifungal prophylaxis in patients with active fungal infection or with persistent radiological abnormalities remains unclear.

Additional well-designed studies of primary and secondary antifungal prophylaxis are needed, not only to evaluate the efficacy of new antifungal drugs, but also to define risk stratification criteria and tailored prevention strategies in the different clinical settings of the hematologic disorders.

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