Prophylaxis of mould infections

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ABSTRACT

Invasive fungal infection continues to be an important cause of morbidity and mortality in haematological patients. Antifungal prophylaxis in these patients has remarkably increased survival since its introduction. In recent years, new antifungals have been on the rise, being more effective and having less toxicity than previous ones. Nonetheless, the number of patients at risk of fungal infection has also been increasing due to the continuous appearance of new immunosuppressive treatments. As a result of such, we face a changing situation that requires constant updating.

Key words: antifungal prophylaxis, invasive fungal infection, haematological malignancies, haematopoietic stem cell transplant.

INTRODUCTION

Invasive fungal infection (IFI) is currently one of the main causes of infectious mortality in haematopoietic stem cell transplantations (HSCT) and an important cause of morbidity and mortality in onco-haematological patients, mainly those affected by acute leukaemia and myelodysplastic syndromes treated with intensive chemotherapy. The frequency of cases of IFI varies considerably per the underlying disease and treatment administered.

In past decades, there has been a decrease in mortality by invasive aspergillosis (IA) due to earlier diagnosis and new antifungal agents. Nonetheless, the number of patients at risk of fungal infection has experienced an increase due to host defence impairment secondary to intensive chemotherapies and corticosteroid use, longer survival of HSCT, new other

immunosuppressive agents and the recognition of new susceptible host such as those with severe influenza infections.

In light of such scenario, IFI prevention should be made priority objective in at-risk patients, especially onco-haematological and HSCT recipients. Although prevention can be approached in several ways, chemoprophylaxis will be our primary focus. The aspects of antifungal chemoprophylaxis that will be presented in depth as follows: patients at risk of IFI caused by moulds, indications for prophylaxis and antifungals agents used.

PATIENTS AT RISK OF INVASIVE FUNGAL INFECTION CAUSED BY MOULDS

Table 1 summarizes the patients with the highest risk of mould infection. One of the highest risk groups of IFI is HSCT recipients. In an American prospective surveillance multicentre study of IFI in HSCT recipients, Kontoyiannis et al [1] describe

Table 1	Patients at high risk of mould infection
Patients at risk of invasive pulmonary aspergillosis	
Acute myeloid leukaemia	
Allogenic HSCT recipients	
Moderate and severe GVHD	
Prolonged neutropenia	
Other haematological malignancies with biological therapies	
SOT recipients (especially heart and lung)	
PCNSL receiving ibrutinib	
Influenza A (H1N1) infection (especially in immunocompromised patients)	

HSCT: haematopoietic stem cell transplantation. GVHD: graft versus host disease. SOT: solid organ transplant. PCNSL: Primary central nervous system lymphoma.

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that the total incidence of IFI did not decrease in spite of common practice with antifungal prophylaxis. They observed that cumulative incidences of aspergillosis increased, whereas invasive candidiasis remained stable. This fact is probably due to current prophylaxis, by which most include fluconazole, without action against moulds.

Another classic group of at-risk patients is solid organ transplantation (SOT) recipients. In a transplant-associated infection surveillance study, Pappas et al [2] observed a slight increase of IFIs during this period, differing according to the type of organ transplantation performed. The increase in IFIs was reflected mainly in the increase in the incidences of *Candida* infections, whilst cumulative incidence of *Aspergillus* infections remained unchanged. Neofytos et al [3] observed that invasive aspergillosis remains a rare complication post-SOT with atypical radiographic presentations and low positive rates of biomarkers. The incidence of invasive aspergillosis was higher in lung (8.3%) and heart (7.1%) transplantation recipients. The median time between transplantation and invasive aspergillosis was 100 days; it was shorter in heart and liver transplantation cases (median 11 and 18 days, respectively). Overall mortality decreased in SOT recipients, but remained high in liver SOT recipients.

In recent years, numerous studies have been conducted to identify risk factors for IFI, but only a few have been made to assess the real incidence in non-transplantation patients with haematological malignancies. Pagano et al [4] reported that amongst non-transplanted patients, those with acute myeloid leukaemia had the highest risk of IFI: about 8% of acute myeloid leukaemia patients would develop mould infections, mainly aspergillosis, and 4%, yeast infections. Almost half of these infections emerged during the first course of induction chemotherapy. IFI-attributable mortality rate was 39%.

Until now, little information was available concerning incidence of IFIs in chronic lymphoproliferative disorders. Novel treatments like immunomodulating and immunosuppressive agents in addition to cytotoxic treatments have increased the risk of IFIs amongst these patients. A recent paper described that IFI in lymphoproliferative disorders has a cumulative incidence of up to 14% in patients with multiple myeloma and 7.8% in patients with chronic lymphocytic leukaemia [5].

Primary central nervous system lymphoma (PCNSL) is an aggressive type of lymphoma with a poor prognosis. The combination of temozolomide, etoposide, doxorubicin, dexamethasone, rituximab, and ibrutinib (DA-TEDDi-R) induced frequent responses, but was associated with aspergillosis infections. Previous studies have reported an incidence of invasive aspergillosis ranging from 5 to 11% using single-agent ibrutinib; incidence increased to 39% when treatment was combined with DA-TEDDi-R [6]. It is tempting to speculate that the concomitant use of ibrutinib and steroids may increase the incidence of aspergillosis. Therefore, one may consider antifungal prophylaxis in patients with PCNSL receiving ibrutinib if this treatment regimen becomes standard.

In another scenario, influenza A infection has been reported to possibly predispose patients with such infection to invasive aspergillosis, especially those patients who are immunocompromised (frequency was 8.8% in patients with acute myeloid leukaemia and transplant recipients) [7]. Schauwvlieghe et al [8] measured the incidence of invasive pulmonary aspergillosis in patients with influenza pneumonia in the intensive care unit. Incidence was 32% and 14% in immunocompromised and non-immunocompromised patients, respectively; and it was associated with high mortality. Influenza was found to be independently associated with invasive pulmonary aspergillosis.

PREVENTION OF INVASIVE FUNGAL INFECTIONS

To date, antifungal prophylaxis is indicated in high-risk haematological patients, those with acute myeloid leukaemia and allogenic stem cell transplants. Most experience in antifungal chemoprophylaxis has been with azole agents. The main studies with the different azole agents are summarised in table 2.

Cornely et al [9] designed a randomised and multicentre study to compare the efficacy and safety of posaconazole as prophylaxis (n=304) in relation to fluconazole or itraconazole (n=240) in patients undergoing chemotherapy for acute myelogenous leukaemia or myelodysplastic syndrome. The group undergoing prophylaxis with posaconazole was superior to those groups undergoing prophylaxis with fluconazole or itraconazole with respect to the prevention of proven or probable invasive fungal infections (2% vs 8%, p<0.001, had significantly fewer invasive aspergillosis (1% vs 7%, P<0.001) and resulted in lower mortality from any cause (16% vs 22%, P=0.048) and longer free survival from proven or probable invasive fungal infection. There were more serious adverse events related to treatment in the posaconazole group (6% vs 2%, P=0.001). The estimated number needed to treat with posaconazole to prevent one IFI, as compared with fluconazole or itraconazole, was 16 patients; and to prevent one death, 14 patients.

In an international, randomised, double-blind trial, Ullman et al [10] compared oral posaconazole (n=301) with oral fluconazole (n=299) for prophylaxis against invasive fungal infections in patients with graft-versus-host disease who were receiving immunosuppressive treatment. Posaconazole was found to be as effective as fluconazole in preventing all IFIs (5.3% vs 9%, P=0.07) and was superior to fluconazole in preventing invasive aspergillosis (2.3% vs 7%, P=0.006). Overall mortality was similar in both groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1% vs 4%, P=0.046). The incidence of adverse events was similar in both groups. The estimated number needed to treat with posaconazole to prevent one IFI was 27 patients.

Wingard et al [11] conducted a randomised, double-blind, multicentre study to compare fluconazole (n=295) versus voriconazole (n=305) as IFI prophylaxis in patients undergoing HSCT within the context of a structured fungal screening

| Table 2 | Most important antifungal prophylaxis randomized studies in high risk haematological patients. |

Authors	Patients	Antifungal prophylaxis	Results	Others
Cornely et al [9]	Acute myelogenous leukaemia or the myelodysplastic syndrome undergoing chemotherapy	Posaconazole (304) vs fluconazole (240) or itraconazole (58)	Posaconazole was superior in the prevention of IFI (p<0.001) and had lower mortality than any other cause (p=0.048)	More serious adverse events in posaconazole group (p=0.01)
Ullman et al [10]	GVHD who were receiving immunosuppressive treatment	Posaconazole (n=301) vs fluconazole (n=299)	Posaconazole was as effective as fluconazole in preventing all IFI (p=0.07)\n\nPosaconazole was superior in preventing invasive aspergillosis (p=0.006).\n\nOverall mortality was similar, but lower due to invasive fungal infections in the posaconazole group (p=0.046).	Adverse events were similar.
Wingard et al [11]	Patients undergoing HSCT	Fluconazole (n=295) vs voriconazole (n=305)	Voriconazole trends to be more effective in preventing IFIs (p=0.12) and *Aspergillus* infections (p=0.09).\n\nNo differences in fungal-free survival at 6 months and overall survival	Severe adverse events were similar.

IFI: invasive fungal infection. GVHD: graft versus host disease. HSCT: haematopoietic stem cell transplantation

programme. Methods used in this study differ from those used in posaconazole trials given that most of the researchers had conducted trials evaluating itraconazole. Those studies showed trends in reduction in frequency of invasive *Aspergillus* infection, but without any clear survival benefits; concerns about tolerability and toxicities were raised. The primary endpoint for Wingard study was therefore freedom from IFI or death at 180 days. Despite the trend of fewer cases of IFIs (7.3% vs 11.2%; P=0.12), *Aspergillus* infections (9 vs 17; P=0.09), and less frequent empiric antifungal therapy (24.1% vs 30.2%; P=0.11) with voriconazole, fungal-free survival rates (75% vs 78%; P=0.49) at 180 days were similar with fluconazole and voriconazole, respectively. Relapse-free and overall survival, as well as the incidence of severe adverse events were also similar. Even though most data on IFI incidence was very much similar to that reported by Ullman, these authors detailed that fungal-free survival at 6 months and overall survival did not differ between fluconazole or voriconazole prophylaxis.

Voriconazole is an important and excellent therapeutic agent; however, due to adverse effects, it necessitates close monitoring, particularly in immunocompromised hosts receiving the drug for a prolonged period. Well-known effects are hepatotoxicity (12-20%), visual disturbances (20-30%) and phototoxicity. Although it is also related with skin cancers (OR 2.6), cardiac arrhythmias, QT Interval prolongation, periostitis (20-25%), central (hallucinations 14%) and peripheral system adverse effects (9%), alopecia and hyponatremia. It will therefore be important to avoid prolonged prophylactic treatments [12]. In addition, in data sheets, voriconazole is contraindicated for patients being administered sirolimus, an immunosuppressive therapy very common used in transplant recipients.

Recently, clinical guidelines for the management of invasive diseases caused by *Aspergillus* have been published by GEMICOMED (Medical Mycology Study Group), REIPI (Spanish Network of Infectious Pathology Investigation), and SEIMC (Spanish Society of Clinical Microbiology and Infectious Diseases). In summary, prophylaxis with an anti-mould agent is recommended for invasive aspergillosis prevention in patients with acute leukaemia; prolonged and profound neutropenia; allogeneic HSCT recipients during the neutropenic phase; and those with moderate to severe graft versus host disease and/or intensified immunosuppression (AI). Antifungal drugs which can be used in high-risk patients include: posaconazole (AI), voriconazole (AI), itraconazole (BII), micafungin (BIII), caspofungin (CIII), aerosolized L-amphotericin B (BI) and intravenous lipidic formulations of amphotericin B (CII) [13]. These authors recommend the use of posaconazole as a first line antimould prophylaxic treatment.

WHY IS POSACONALE SO EFFECTIVE IN PROPHYLAXIS?

Tissue penetration into the site of infection to achieve microbial kill concentrations is a key requirement for efficacy. Posaconazole has much larger volumes of distribution in contrast to voriconazole and high plasma protein binding (>98%). Posaconazole penetrates preferentially into tissue with high lipid content and that which often exhibits tissue/plasma concentration ratios which exceeds 1. This drug exhibits epithelial lining fluid concentration similar to that seen in plasma, but the exposure in alveolar cells is 30 times more than that in plasma [14].

Pharmacokinetic (PK)/pharmacodynamic (PD) parameters

related with efficacy in antifungals are area under the concentration-time curve (AUC)/minimum inhibitory concentration (MIC). Drug peak serum concentration above MIC explains the continued concentrations within the tissue. Therefore, it has been suggested that high intracellular posaconazole concentrations may account for prophylaxis effectiveness.

Isavuconazole is a novel broad-spectrum triazole agent with a safety profile and similar PK/PD parameters to posaconazole, with its indication for treatment of IFI being nowadays restricted due to the lack of clinical experience. Studies on the PK/PD of isavuconazole demonstrated that bioavailability is very high and plasma protein binding is around 98%. It has a large volume of distribution and a long half-life. This, in turn, offers potential for use in fungal prophylaxis, salvage therapy or in combination regimens [15]. However, no current studies demonstrating the efficacy of isavuconazole in preventing IFI in high-risk populations has been conducted.

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