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Prophylactic Strategies for Invasive Fungal Diseases in Hematological Stem Cell Transplantation: An Update

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Abstract

Patients that have received hematopoietic stem cell transplantation are at increased risk for a myriad of infectious complications including invasive fungal infection (IFI). These patients face high morbidity and mortality due to difficulty in diagnosis, which lead to delayed treatment. Various prophylactic strategies have been proposed in the past. This article reviews evolving guidelines from various professional organizations so as to facilitate optimization of clinical decision. (J Intern Med Taiwan 2018; 29: 38-45)

Key Words: Hematopoietic stem cell transplantation, Invasive fungal infection, Aspergillosis, Antifungal agents

Introduction

Fungal infection is a cause of significant morbidity and mortality in patients undergoing hematopoietic stem cell transplantation. Despite recent advances in diagnostic methods, exactly how these diagnostic methods should be employed remains a topic of debate. Diagnosis of fungal infection remains difficult, resulting in delayed treatment and worsened outcome. As such, prophylactic strategies against fungal infections are crucial, especially in high-risk situations. In 2009, a comprehensive guideline for the prevention of infectious complications among hematopoietic cell transplantation recipients (HSCT) was published by the American Society for Blood and Marrow Transplantation (ASBMT)[1]. Since then, a number of other countries have published their own guidelines regarding prophylaxis of fungal infections among HSCT recipients. This review summarizes recent advances in the prophylactic strategies of invasive fungal infections in HSCT patients, with special emphasis on international guidelines that have been published since 2009.

Epidemiology and Risk

Candida

As normal commensal of mucosal surfaces, *Candida* species have long played a significant role in invasive fungal infections, afflicting hematopoi-

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etic stem cell recipients particularly when mucosa is damaged. In the 1980s and 1990s, invasive candidiasis is a relatively common invasive fungal infection among this patient population. With the widespread use of azole prophylaxis, it has become less common; the causative *Candida* species has also changed[2]. For patients undergoing allogeneic hematopoietic transplantation, the incidence of candidemia ranged from 0.51% to 4.6%[3-6]. In a study in China involving 408 patients, the incidence of candidiasis was 12.3%[7] whereas candidiasis was found to be 4.0% in a medical center in Taiwan[8] . For autologous patients, the incidence of candidemia was lower; documented at 0.8%[3] in one study and 0.4%[4] in another. Incidence of candidiasis post autologous HSCT in Taiwan is unknown due to lack of study. In a study performed by The Transplant Associated Infections Surveillance Network, a network of 23 US transplant centers, 875 HSCT recipients with 983 proven and probable IFIs occurring between March 2001 and March 2006 were enrolled. Of the 276 patients with invasive candidiasis, *Candida glabrata* was the most common organism isolated (33%), followed by *Candida albicans* (20%)[9]. In a study from the North American PATH Alliance registry, sixteen medical centers reported data on adult HSCT recipients with proven or probable IFD between July 2004 and September 2007. *C. glabrata* was the most common species (43.5%) isolated, with *C. albicans* accounting for 24.4% and *Candida krusei* accounting for 11.3% (four cases).[10]

Aspergillus

Due to the widespread use of fluconazole as antifungal prophylaxis, the incidence of invasive *Candida* infections has decreased, with mold infections increasingly playing a greater role post HSCT. This is especially true following allogeneic transplantation. A bimodal occurrence of invasive aspergillosis after transplantation has been observed, with risks highest in the early (pre-engraftment, median 16 days after transplant) and late (postengraftment, median 96 days after transplant) periods[11]. Incidence of invasive aspergillosis has been reported in 10-20% in allogeneic HCT recipients and in up to 2% of autologous HCT recipients[6,12]. A study in Tri-State General Hospital in Taiwan estimated the incidence of aspergillosis to be at 20%[13] among HSCT patients with mechanical ventilation in the intensive care unit. Another study performed at Veterans General Hospital in Taiwan estimated the incidence of aspergillosis post allogeneic transplantation to be at 2.1%[8].

Other fungal species

Infections with other fungal species have been observed, including *Acremonium* spp, mucormycosis, *Trichosporon* species, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, *Geotrichum candidum*[4,6,8]. Of note, the incidence of zygomycosis has increased significantly in recent years, which is primarily attributable to the use of voriconazole, since it was active against *Aspergillus* but not against Zygomycetes[14].

Antifungal Agents

Fluconazole

Owing to its good tolerability, low cost and the availability in both intravenous and oral forms, fluconazole is generally still considered the drug of choice across many guidelines[1,2,15] in the prophylaxis of *Candida* infection, reducing the incidence of candidiasis and mortality rate after allogeneic hematopoieic stem cell transplant[16]. However, it has relatively narrow spectrum of activity and is only active against yeasts. Among *Candida* species, it has limited efficacy against *C. glabrata* and *C. krusei* [17]. Since azoles are inhibitors of the CYP P450 isoenzymes, drug interaction effects must be taken into consideration when prescribing fluconazole.

Voriconazole

The second-generation triazole has the advantage of being mold-active in addition to being effective against yeasts. It can also be administered in both oral and intravenous forms. In a recent large meta-analysis, antifungal prophylaxis with voriconazole decreased transplant mortality compared with fluconazole or itraconazole[18]. In terms of spectrum of activity, its most significant limitation is its lack of activity against zygomycetes. Voriconazole has several significant adverse side effects, including hepatotoxicity, nausea, vomiting, diarrhea, visual changes, ventricular extra systoles, and dizziness[19]. Its serum concentration may be unpredictable and therapeutic drug monitoring (TDM) should generally be undertaken to ensure efficacy. Efficient antifungal treatment can be achieved with a wide range (0.35–2.2 mg/L) of voriconazole although concentrations with an optimum range of 1–2 mg/L may be considered optimal, as the voriconazole MIC for most fungi is 0.5–1 mg/L[20]. It should be taken without food.

Posaconazole

Posaconazole has an extended spectrum of activity and is active against most frequently isolated yeast and mold pathogens, including *Candida, Aspergillus, Cryptococcus, Zygomycetes,* and *Fusarium*. Two guidelines by the ASBMT and by the Infectious Diseases Working Party of the German Society for Haematology and Oncology[1,16] both recommended its use as prophylaxis of IFIs in patients with graft-versus-host disease (GVHD). It is currently available in three dosage forms, including an oral suspension form, a delayed-release tablet form, and an intravenous form. The oral suspension form is limited by the fact that the highest plasma levels are reached when taken with fat-rich food. Absorption is impaired in patients who are fasting, who have diarrhea, those with gastrointestinal mucositis due to chemotherapy or GVHD or in patients taking proton pump inhibitors. The US Food and Drug Administration (FDA)- recommended serum posaconazole concentration is 0.7 mg/L[21]. The extended-release tablet form of posaconazole was approved by the FDA in November 2013. It is notable that these two different formulations cannot be directly substituted for each other but require a change in dose. Direct mg-for-mg substitution led to drug levels that were lower or higher than therapeutic level, resulting in death and hospitalization[22]. Posaconazole has safety profile that is generally comparable to that of fluconazole[23,24], and has lower potential for drug-drug interactions than voriconazole or itraconazole[25].

Itraconazole

Itraconazole has a broad spectrum of activity, being active against *Candida, Cryptococcus*, dermatophytes, *Aspergillus*, and dimorphic fungi[26]. *C. glabrata* and *C. krusei* exhibit variable resistance to itraconazole. Under the 2009 guideline, it is listed as an alternative antifungal agent to fluconazole in patients with standard risk for fungal infections, namely those who have undergone allogeneic HCT or those having received autologous HCT who have or will have prolonged neutropenia, mucosal damage from intense conditioning regimens, graft manipulation, or who have recently received purine analogues1. Side effects of itraconazole include gastrointestinal toxicity, gynecomastia and adrenocortical insufficiency[21]. Itraconazole has many drug-drug interactions. Co-administration of itraconazole and vincristine may lead to life-threatening visceral neurotoxicity with ileus[27] and increased vincristine-associated neurotoxicity due to increased efflux of vincristine across the blood-brain barrier[28]. Itraconazole also exhibits significant hepatotoxicity when co-administered with cyclophosphamide[24]. Absorption of itraconazole solution is affected by food, as higher bioavailability is achieved under fasting conditions. Itraconazole capsule and tablet absorption is best if taken with food. As such, therapeutic drug

monitoring is recommended for oral formulations[29].

Micafungin

The echinocandins are gaining in popularity in Taiwan due to its favorable toxicity and drug-drug interaction profile. Of the echinocandins, micafungin is the only drug identified to be beneficial for primary antifungal prophylaxis in the neutropenic phase of HSCT by a composite endpoint[21]. Micafungin is active against *Candida* and *Aspergillus* and is suggested in the 2009 guideline as an alternative therapy to fluconazole in the prophylaxis of patients with standard risk against fungal infections, namely those with allogeneic HSCT or those who with prolonged neutropenia and mucosal damage post autologous HSCT[1]. Due to its lack of activity against *C. neoformans*, *F. solani*, *P. boydii*, *Trichosporin*, and the *Zygomycetes*, it is not considered broad spectrum and should not be used when patients are at high risk for mold infections[29]. Currently, the other echinocandins available in Taiwan, including caspofungin and anidulafungin, are not approved by the US Food and Drug Administration for prophylactic use in HSCT.

Prophylactic Strategies

Due to the heterogeneous nature of patients undergoing stem cell transplantation, deciding on an appropriate prophylactic regimen for invasive fungal infection can be challenging. Patients differ in their underlying hematological disease, treatment regimen, and treatment center. Different degrees of immunocompromise predispose patients to infection by different fungal organisms. In addition, drug-drug interactions need to be taken into consideration when administering prophylactic medications along with other concomitant medications. As such, the choice of antifungal prophylaxis should be made case-by-case, which is reflected in the published consensus guidelines.

Primary Prophylaxis

Autologous HSCT

Patients who have undergone autologous hematopoietic stem cell transplant are not considered at high-risk for invasive fungal diseases[15,30]; as such, routine antifungal prophylaxis is not recommended[15,30]. Patients who have increased risk for fungal infection are those who have or will have prolonged neutropenia and mucosal damage from intense conditioning regimens, graft manipulation, or who have recently received purine analogues[1]; in those situations fluconazole is recommended[1]. Prophylaxis is recommended from the start of conditioning (or day of transplantation for advanced-generation azoles) until engraftment (ie, approximately 30 days after HSCT) or until 7 days after the absolute neutrophil count >1000 cells/mm^3. Other authors have suggested that antifungal prophylaxis be discontinued once the neutrophil count has recovered (absolute neutrophil count 500/mm^3) [21].

Allogeneic Transplantation

Patients who have undergone allogeneic transplantation are at risk for fungal infection with both yeasts and molds. The risk differs across time and with different regimens administered, and hence risk stratification according to risk factors is an important consideration in administering prophylactic antifungal agent. To this end, a few professional organizations have recently proposed comprehensive prophylactic antifungal management strategies.

The 2014 Italian Group for Bone Marrow Transplantation risk stratified recipients of allogeneic HCT into high, standard, and low risks based on timing after transplantation and numerous risk factors[2]. During the early phase after transplantation (day 0 - 40), high risk patients are those who have had active acute leukemia at the time of transplantation, transplantation with cord blood, Grade

III-IV acute GVHD after any type of transplantation, steroid refractory / dependent acute GVHD after any type of transplantation, or transplantation from mismatched related or unrelated donor and one or more of the additional risk factors including grade II acute GVHD, steroid dose ≥2 mg/kg/day for at least one week, CMV disease, recurrent CMV infection, prolonged neutropenia as defined by PMN < 500/μL for more than 3 weeks, or iron overload[2]. During this period, all remaining patients not included in the high-risk category are considered at standard risk. In the late phase after transplantation (day 41 - 100), high risk patients are those with acute grade III-IV GVHD, steroid refractory / dependent acute GVHD, or transplantation from a mismatched related donor (MMRD) or unrelated volunteer donor (UD) and 1 or more of the following additional risk factors: grade II acute GVHD, steroid use ≥2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, recurrent neutropenia as defined by PMN < 500 /μL for more than 1 week. All remaining patients are considered at standard risk in this time period. In the very late phase after transplantation (day > 100), patients at high risk are those with persistent or late-onset grade III-IV acute GVHD, persistent or late-onset steroid refractory / dependent acute GVHD, persistent or late-onset grade II acute GVHD after transplantation from MMRD or UD, and extensive chronic GVHD when preceded by an acute GVHD. Patients at standard risk in this time period are those with limited chronic GVHD in patients who receive only a non-steroid immunosuppression and "de-novo" chronic GVHD. Patients at low risk in this period are those with absence of any type of GVHD and no steroid therapy. Those patients with high risk should receive mold-active primary antifungal prophylaxis with posaconazole in GVHD, with TDM advised for oral solution, voriconazole (TDM advised), liposomal amphotericin B, caspofungin, micafungin, or aerosolized amphotericin B plus fluconazole[2]. Those at standard risk are advised to receive *Candida* active primary antifungal prophylaxis using fluconazole, voriconazole, itraconazole or micafungin. No primary antifungal prophylaxis is advised for those with low risk[2].

A slightly simplified algorithm is presented in the 2014 Australasian consensus guideline for antifungal prophylaxis in hematological malignancy and hematopoietic stem cell transplantation[15]. In this guideline, patients are classified into high, low and very low risk categories with mold-active prophylaxis, anti-*Candida* prophylaxis, and no prophylaxis being recommended, respectively. Those at high risk are patients with severe GVHD, defined as steroid dependent or refractory or grades 3 or 4; extensive chronic GVHD, and allogeneic HSCT with expected neutropenia >14 days. Low risk patients are recipients of autologous HSCT with high risk of mucositis, such as those with recent aggressive salvage chemotherapy or receiving multi-agent regimens; and allogeneic HSCT recipients with expected neutropenia <14 days. All other patients are considered at very low risk[15]. A stream-lined presentation of recommendations from the prior guidelines are summarized in Table 1.

Most recently, Pagano[31] identified several risk factors that placed patients at increased risk for invasive fungal infection. These risk factors included advanced age (with no specific threshold defined), underlying AML, lymphomas, iron overload (with no specific defining threshold), alternative donors, polymorphisms in genes such as TLR-4, dectin-1 or pentraxin when associated with high-risk transplants such as matched unrelated donor or haplo; GVHD and immunosuppressive treatments such as steroids, basiliximab, alemtuzumab, ATG and infliximab; CMV infection, and high environmental *Aspergillus* spp. spore[31]. This article did not offer management suggestions.

In the 2012 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) treatment guideline for the diagnosis and manage-

Table 1. Summary of recommendations for prevention of invasive fungal diseases in HSCT patients

Autologous	
Sub-Group	Drug
Patients with High Risk of Mucositis	Fluconazole
All other patients	Routine antifungal prophylaxis not recommended
Allogeneic - Indications for Mold-active Agents	
Active acute leukemia at the time of transplantation[a]	
Transplantation with cord blood (post-transplantation Day 0 - 40)[a]	
Grade III-IV acute GVHD	
Steroid refractory / dependent acute GVHD	
Transplantation from mismatched related or unrelated donor and one or more of the additional risk factors (Post-Transplantation Day 0 - 100): [a]	
● Grade II acute GVHD	
● Steroid dose ≥2 mg/kg/day for at least one week	
● CMV disease	
● Recurrent CMV infection	
● Prolonged neutropenia (PMN < 500/μL > 3 weeks)	
● Iron overload (post-transplantation Day 0-40 only)	
Persistent or late-onset grade II acute GVHD after transplantation from MMRD or UD (Post-Transplantation Day > 100)	
Extensive chronic GVHD, with[a] or without[b] prior acute GVHD	
Allogeneic - Indications for Candida active agents	
All patients Day 0 - 100 Post Transplantation not in high-risk categories as named above[a]	
Patients Post 100 Days of Transplantation with new-onset chronic GVHD and not under steroids[a]	
Allogeneic HSCT with expected neutropenia <14 days[b]	

CB, cord blood; GVHD, Graft-versus-host disease; CMV, cytomegalovirus, PMN, polymorphonuclear neutrophil, MMRD, mismatched related donor; UD, unrelated donor, a indicates recommendations from Girmenia[2] only, b indicates recommendations from Fleming[15] only.

ment of *Candida* Diseases in adults with hematological malignancies and after hematopoietic stem cell transplantation, antifungal agents received different grade of recommendations according to time period post transplantation. In the early neutropenic phase post transplantation, fluconazole, posaconazole, voriconazole, and micafungin received grade A recommendation for reduction of morbidity, but only fluconazole exhibited survival advantage. During the first 100 days post transplantation without GVHD and neutrophil recovery, grade A recommendations were given to fluconazole and voriconazole in terms of reduction of morbidity, but again, only fluconazole demonstrated survival advantage. Finally, for anti-*Candida* prophylaxis in GVHD, fluconazole and posaconazole conferred benefit in reduction of morbidity, and no antifungal agent received A recommendation for survival advantage. The authors gave grade B recommendation for posaconazole during this time period[30].

Secondary Prophylaxis

Secondary prophylaxis is recommended in patients with documented history of suspected or confirmed invasive fungal disease[15], especially with prior invasive aspergillosis[1] or with history of deep-seated invasive *Candida* disease, but not candidemia alone[30]. It is generally accepted that the antifungal medication used to treat the initial infection should be used as secondary prophylaxis[15,21], and a thera-

peutic dosage should be used[15]. Voriconazole has also been found beneficial for this indication[32].

Conclusion

In treating patient population post hematopoietic transplantation, choosing appropriate prophylactic regimen, early diagnosis and effective treatment of fungal infection is crucial to the optimization of outcome. A number of guidelines by multiple professional organizations have been published in literature. Clinician must choose antifungal regimen that is most suitable for the individual patient based on the patient's underlying disease, treatment regimen and clinical condition. Local epidemiology, drug toxicities and drug-drug interactions must be taken into consideration.

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造血幹細胞移植患者真菌感染的預防策略

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摘 要

造血幹細胞移植患者由於免疫系統機下容易發生感染，包括侵襲性真菌感染。這些患者面臨很高的發病率和死亡率。由於難以診斷，因此真菌感染容易被延誤治療。本文回顧近期各專業機構的預防指南，以提供臨床工作者可以做更好的臨床決策。