

Long-term antifungal prophylaxis in high-risk hematopoietic stem cell transplant recipients

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The risks for invasive fungal infections, particularly mould infections such as invasive aspergillosis, among hematopoietic stem cell transplant (HSCT) recipients are linked to the duration and severity of myelosuppression and immunosuppression. Strategies to prevent invasive fungal infections have focused primarily on the use of orally administered azole antifungal agents during the neutropenic period rather than on the more prolonged post-engraftment period. The major limitations of these studies included the heterogeneity among the subjects studied for fungal infection risk factors, the agents administered, the dosing, and duration of prophylaxis. More recent studies have attempted to examine the efficacy of antifungal prophylaxis strategies among allogeneic HSCT recipients to day 100 and beyond. It is clear that a variety of products have efficacy in preventing invasive candidiasis, including imidazole and triazole antifungals, low-dose amphotericin B, and the echinocandin, micafungin; however, only the extended spectrum azole, itraconazole, has been shown to impact the incidence of proven invasive aspergillosis. Other extended spectrum azole antifungal agents, voriconazole and posaconazole, are being studied as long-term prophylaxis in high-risk HSCT recipients. While clinical trials have suggested that a duration of prophylaxis against moulds of six months or more may be required, it remains unclear if this is required in all cases. The prophylactic efficacy over time may be linked to the degree of immunosuppression as measured by markers such as the numbers of circulating CD4 T lymphocytes. Concerns about selection for resistant moulds among long-term recipients of these drugs are emerging. The cumulative experience to date suggests that long-term antifungal chemoprophylaxis is feasible and effective when applied in defined circumstances. The concerns about treatment-related toxicities, resistance, and costs are valid.

Keywords antifungal chemoprophylaxis, antifungal resistance, econotoxicities, hematopoietic stem cell transplant, risk

Introduction

The recognition and management of invasive fungal infection (IFI) represent some of the most difficult

challenges facing supportive care strategies for hematopoietic stem cell transplant (HSCT) recipients. The risks, incidence, types, and natural history of IFI are not uniform among all transplant patient populations. A clearer understanding of these differences permits a more rational approach to the development and application of successful preventative strategies.

The overall incidence of IFI among high-risk allogeneic HSCT recipients has ranged between 10% and

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25% [1–5]. Invasive aspergillosis (IA) in this patient population has a bimodal time of onset, the first during the pre-engraftment neutropenic period and a second during the post-engraftment period (median day +65) with a range of onset that varies with other processes such as late onset neutropenia, cytomegalovirus disease, and graft-versus-host disease (GVHD) that may develop during this time [1]. The cumulative one-year incidence of IFI for HSCT recipients conditioned by non-myeloablative (NMA) regimens may be as high as 19% (moulds, 15%; and invasive candidiasis, 5%), which appears to be similar to that for conventional myeloablative (MA) allogeneic HSCT [6]. The onset of invasive mould infections (IMI) following NMA-HSCT has been later in post-engraftment period at day +107 (range day +4 to +282) [6].

In contrast, IFI rates are much lower among autologous HSCT recipients, in the range of 1% to 2% [7–12]. However, rates may be as high as 5%, particularly for IA, among patients receiving bone marrow as the source of autologous stem cells [13–15]. IA, like invasive candidiasis, has a unimodal pattern of onset during the third week post-transplant in this patient population [1].

Guidelines governing the use of antifungal prophylaxis in HSCT patients have been published [16–19]. However, the extent to which antifungal prophylaxis is prescribed among these patients is unclear. A recent survey among 31 transplant centers in the United States and Mexico demonstrated that antifungal prophylaxis was prescribed for 90% and 94% of autologous and allogeneic HSCT recipients, respectively [20]. Among those centers utilizing antifungal chemoprophylaxis, fluconazole was prescribed in 93% and 72%, itraconazole in 3.5% and 14%, and amphotericin B in 3.5% and 14%, for autografts and allografts, respectively. Prophylaxis began with the start of conditioning in all but one case and continued among autografts until neutrophil engraftment (absolute neutrophil count $\geq 0.5 \times 10^9/\text{L}$) and among allografts until neutrophil engraftment in 21% of patients, beyond engraftment from day +75 to day +180 in 28% of patients, and until cessation of immunosuppression in 45% of patients [20]. These observations underscore the limitations in prophylaxis efficacy for moulds such as *Aspergillus* spp. and the variability in the duration of administration.

Risk factors for invasive mould infections

The risk for IFI in cancer patients varies with the degree and severity of neutropenia, the underlying

diagnosis, the cytotoxic or immunosuppressive regimen administered to treat the underlying cancer, and the circumstances of responsiveness of the underlying neoplasm for which the treatments are administered [21]. Other categories of predictors associated with the risk of fungal infection-related morbidity include advanced age [22,23], advanced underlying disease [1,24], myelosuppression [25–27], immunosuppression [1,28], colonization of epithelial surfaces [29–33], environmental exposure [34–44], and physical damage to the integumental surfaces [33,45].

Numerous risk factors for IFI in HSCT have been identified. Prolonged severe neutropenia has been held as one of the most important risk factors for the development of IA [25,27,46] and for mortality [27,47]. Pre-engraftment neutropenia remains a risk factor, particularly for autologous HSCT patients; however, almost one-quarter of allogeneic HSCT recipients who develop IA during neutropenia have the onset during post-engraftment periods of neutropenia [1]. IA and invasive candidiasis have been observed more often in HSCT patients with hematological malignancies not in first remission [1,23]. Transplantation outside of a high-efficiency particulate air-filtered environment confers a risk for mould infection [1] and transplant-related mortality [48]. Not only does the type of transplant (allogeneic vs. autologous) correlate with the risk of IFI, but also a low number ($\leq 3 \times 10^6$ CD34 cells/kg versus $> 3 \times 10^6$ CD34 cells/kg) [49] and non-peripheral blood source (cord blood versus bone marrow versus peripheral blood) [50–52] of the transplanted stem cells imparts significant risk. The risks for early IA attributable to stem cell source are largely a function of time-to-neutrophil engraftment [51]. The type of conditioning therapy (total body irradiation [TBI]-based versus non-TBI) [52] and use of CD34-selected/T-cell depleted stem cell products [51] may also play a role. Cytomegalovirus antigenemia and CMV disease with lymphopaenia (absolute lymphocyte count $< 0.3 \times 10^9/\text{L}$) have been reported as independent risk factors for IMI in non-myeloablative HSCT [6]. Marr and colleagues from the Fred Hutchinson Cancer Research Center showed that use of peripheral blood stem cells (PBSC) from unrelated mismatched allogeneic donors was associated with a 65% increase in the incidence of invasive aspergillosis [51]. GVHD (acute, grades II to IV; chronic extensive) and treatment thereof (prednisone $> 1\text{--}2$ milligrams/kg $^{-\text{d}}$) are also recognized as major risk factors for invasive fungal infection in HSCT [1,2,6,51].

Evidence for efficacy of antifungal prophylaxis strategies

The success of a preventative strategy for a given IFI is linked to an understanding of the pathogenesis. Invasive candidiasis is most often associated with translocation across colonized gastrointestinal epithelial surfaces damaged by surgical trauma, cytotoxic therapy or GVH reactions. In contrast, acquisition of invasive mould infections is, for the most part, a function of inhalation of air-borne conidia into the upper and lower respiratory tract whereupon germination and invasion follows in the setting of impaired cellular defenses. Most chemoprophylaxis strategies have focused upon the administration of antifungal agents that can reduce mucosal colonization by fungi and thereby limit the size of the pool of possible invading pathogens as in the case of opportunistic yeasts or by limiting germination of conidia on respiratory mucosal surfaces [53].

Exposure to air-borne conidia can be reduced by management of high-risk patients in protective environments utilizing high-efficiency particulate air-filtering systems with or without laminar air-flow [42,43]. A systematic review of randomized-controlled clinical trials of protective environments in a heterogeneous population of neutropenic cancer patients has demonstrated a 52% reduction in clinical pneumonia ($n=1,019$ subjects in 11 randomized-controlled clinical trials, pooled weighted odds ratio [OR] 0.41, 95% confidence interval [CI] 0.28 to 0.61; number needed to treat, 8) [54–64]. Management of high-risk patients in such environments during the pre-engraftment period can reduce the incidence of invasive mould infection [39] and transplant-related mortality [48,65]. While protective environments may be effective for reducing the risk of IMI during severe neutropenia, they are of limited practical value for long-term protection after myeloid reconstitution. For this reason, investigators have focused upon the administration of polyene-, azole-, or echinocandin-based antifungal chemoprophylaxis. The outcomes examined in clinical trials have included reductions in the use of empirical antifungal therapy, proven superficial and invasive fungal infection, mucosal colonization by fungi, overall mortality, and fungal infection-related mortality.

Four systematic literature reviews on antifungal prophylaxis have been published [66–69]. These studies focused primarily on oral or combined intravenous and oral azole-based prophylaxis strategies. The study from the Cochrane collaboration [66] examined 24 trials encompassing 2,758 randomized subjects. This report has been criticized for the inclusion of studies of

empirical antifungal therapy as well prophylaxis studies [69,70]. The study from Japan examined 16 fluconazole-based trials with 3,734 subjects and demonstrated that prophylaxis efficacy was apparent only among studies with high IFI event rates of 15% or more, particularly in HSCT recipients [67]. The Canadian study [68] examined 7,014 randomized subjects in 38 trials analyzing the prophylaxis efficacy of fluconazole, itraconazole, ketoconazole, miconazole, and parenteral amphotericin B compared to placebo or no treatment, or to oral polyenes. This meta-analysis demonstrated overall reductions in the need for empirical antifungal therapy (OR 0.57, 95% CI 0.48 to 0.68), proven superficial (OR 0.29, 95% CI 0.20 to 0.43) and invasive (OR 0.44, 95% CI 0.35 to 0.55) fungal infections, fungal infection-related mortality (OR 0.58, 95% CI 0.41 to 0.82), and in overall mortality among studies with prolonged severe neutropenia (OR 0.72, 95% CI 0.55 to 0.95) and in HSCT-weighted studies (OR 0.77, 95% CI 0.59 to 0.99) [68].

The German study [69] examined 3,597 subjects in 13 trials focusing on itraconazole compared to placebo or no treatment, fluconazole, or to oral polyenes. This analysis included studies with higher-risk patients and was able to demonstrate that itraconazole oral solution was more successful in reducing invasive fungal infections due not only to opportunistic yeasts (OR 0.40, 95% CI 0.21 to 0.76) but also due to *Aspergillus* spp. (OR 0.52, 95% CI 0.30 to 0.90) than the itraconazole oral capsule formulation (OR 0.63, 95% CI 0.26 to 1.55 for invasive yeast infections and OR 1.75, 95% CI 0.61 to 5.07 for invasive aspergillosis). One of the studies included in the German meta-analysis [5] demonstrated the important relationship of prophylaxis efficacy and compliance with itraconazole dosing among allogeneic HSCT recipients. Previous studies of itraconazole for the management of IA have suggested that therapeutic efficacy may be a function of minimum serum concentrations [71–73] [Glasmacher *et al.*, ICAAC 2002, abstr M-890]. Both the Canadian and German reviews were able to demonstrate a dose-response relationship effect related to prophylaxis efficacy [68,69]. Bow and colleagues noted that azole-based antifungal prophylaxis regimens required daily doses of more than 200 mg to reduce the risk for invasive fungal infection [68]. A similar observation was made by Glasmacher and colleagues in a more focused examination of prophylactic itraconazole (OR 0.47, 95% CI 0.31 to 0.70) [69].

The Canadian study [68] also examined the prophylaxis efficacy of lower-dose intravenous amphotericin B formulations in neutropenic HSCT patients in four placebo-controlled trials encompassing a total of

454 randomized subjects [74–77]. Prophylaxis was more successful (OR 1.61, 95% CI 1.09 to 2.38) and fewer proven IFI (OR 0.22, 95% CI 0.08 to 0.58) were observed among prophylactic amphotericin B recipients, respectively, than among placebo recipients. Treatment effects were not observed for superficial fungal infections, overall mortality, or for fungal infection-related mortality. Amphotericin B-based prophylaxis strategies, while effective for reducing the risks of IFI, still suffer from the limitations of requiring intravenous administration, from the known metabolic and infusion-related toxicities, and from the costs associated with the lipid-formulations.

A large study of the prophylaxis efficacy of the echinocandin antifungal agent, micafungin, compared to fluconazole examined a heterogeneous population of 882 HSCT recipients. This study covered only the pre-engraftment neutropenic period. There was a 29% reduction in the need for empirical antifungal therapy ($P=0.018$) and an 86% reduction in the incidence of breakthrough IA ($P=0.07$) among micafungin recipients [78]. These observations suggest that echinocandins may constitute useful alternatives for antifungal prophylaxis; however, the requirement for intravenous administration and the anticipated high costs of these products will likely limit the overall long-term outpatient applicability [79].

Cumulative experience with oral antifungal chemoprophylaxis appears to support the conclusion that these strategies do reduce the incidence of invasive fungal infections due to both yeasts and moulds in high-risk patient populations over the period of risk. Furthermore, in defined subgroups of patients fungal infection-related mortality and even overall mortality is reduced by oral azole-based prophylaxis. Experience with intravenously administered polyenes and echinocandins is more limited; however, the efficacy data are encouraging. The logistics of administration, toxicity profiles and cost issues may limit applicability. The caveats for oral azole-based chemoprophylaxis strategies include the need to pay attention to compliance, select an oral formulation that assures absorption, and be cautious with regard to azole-related drug interactions with cyclophosphamide-based conditioning regimens [80,81] and calcineurin inhibitors [82].

How long is 'long-term' antifungal prophylaxis?

Antimicrobial prophylaxis strategies are by convention applied to patients at risk over the period of risk. The risk factors for invasive fungal infection are well known; however, the time during which any one or

more of these risk factors influence a given patient is less clear. The relationship between infection and myelosuppression as measured from the circulating absolute neutrophil count has long been established [83,84]. The influence of neutropenia as a risk factor for invasive fungal infection can be estimated among HSCT recipients from the expected times-to-neutrophil engraftment associated with the particular conditioning regimen. The longer the period of severe neutropenia, the greater the risk for invasive fungal infection, including IA [27].

The source of stem cells has influenced this risk. The reported times-to-engraftment have been 22 days (range 11–36 days) and 14 days (range 11–29 days) among allogeneic bone marrow and PBSC recipients, respectively [85–89]. Bone marrow as a source of stem cells has been associated with a higher risk of invasive fungal infection (adjusted risk ratio 5.55, 95% CI 1.20 to 25.7) [50]. Furthermore, the dose of CD34⁺ stem cells also plays an important role influencing the time-to-engraftment and risk for invasive fungal infections. Bittencourt and colleagues observed invasive fungal infection rates of 26% and 12% among recipients of CD34-stem cell doses of $<3 \times 10^6/\text{kg}$ and $\geq 3 \times 10^6/\text{kg}$, respectively ($P=0.009$) [49]. While PBSC as a source for allogeneic HSCT has not been associated with undue risks for acute GVHD, there is an increased risk for extensive chronic GVHD (pooled weighted OR 2.16, 95% CI 1.48 to 3.13) [85–89], which, in turn, has been reported to increase the risk for invasive fungal infection, including IA, from 3% to 41% [2].

The absolute monocyte count (AMC) may also be a useful marker of infection risk in cancer patients receiving cytotoxic therapy. Previous studies have examined the relationship of monocytopenia ($\text{AMC} < 0.2 \times 10^9/\text{L}$) and the risk of bacterial infection, predominantly in pediatric patient populations [90–96]. One study in patients with aplastic anemia addressed the correlation between monocytopenia and invasive fungal infection [97]; however, the analysis was confounded by the effects of concomitant neutropenia. Among cancer patients receiving myelosuppressive cytotoxic therapy resulting in pancytopenia, the ability to discriminate the relative contributions of monocytopenia and neutropenia to infection risk is very difficult. This question is better addressed among patients with normal absolute neutrophil counts and monocytopenia. More recently, Storek [98] reported an inverse relationship between persistent B-lymphocytopenia and monocytopenia and the risk of fungal infection following engraftment among allogeneic hematopoietic stem cell transplant recipients that appeared to be independent of the influence of

neutropenia. These observations are consistent with the known role of mononuclear phagocytes in host defense against inhaled conidia and with the observed therapeutic effects of hematopoietic growth factors that affect the mononuclear phagocyte in patients with invasive fungal infection [99–102]. Accordingly, monocytopenia in the absence of significant neutropenia ($\text{ANC} < 0.5 \times 10^9/\text{L}$) may be more important as a risk factor for invasive infection than previously thought.

The quantification of immunosuppression as a risk factor for invasive fungal infection is more difficult. The inverse relationship between the circulating CD4^+ T-lymphocyte count and opportunistic infections such as those due to *Candida* spp. and *Aspergillus* spp. in patients with HIV/AIDS has been well established [28,103–105]. Little attention has been paid to cancer chemotherapy-induced reduction of the absolute lymphocyte count (ALC) and its related subsets with regard to infection risk [106]. Previous reports have described the relationship between use of T cell depletion strategies for the reduction of severe GVHD and invasive fungal infection [107]. An absolute circulating lymphopenia of $< 0.7 \times 10^9/\text{L}$ on day five of cytotoxic therapy has been reported as a predictor for febrile neutropenic episodes among cancer patients [108]. Among patients receiving highly active anti-retroviral therapy for HIV infection resulting in an increase in the circulating CD4 T-lymphocyte count to $> 0.2 \times 10^9/\text{L}$, it has been shown that discontinuance of prophylaxis against pulmonary pneumocystosis is safe [109–115].

Previous studies among HSCT recipients have noted inverse relationships between the CD4 T lymphocyte or B lymphocyte counts and post-engraftment infectious morbidity [98,116,117]. Based upon these observations, it seems reasonable to speculate that markers such as the circulating CD4 T lymphocyte counts or CD19 B lymphocyte counts may be sufficiently useful discriminators for immunosuppression and risk for opportunistic fungal infections, and that they could be employed to guide the duration of antifungal chemoprophylaxis. The duration and magnitude of immunosuppression due to agents such as corticosteroids, the calcineurin inhibitors, mycophenolate mofetil, azathiaprine, or anti-thymocyte globulin administered for the management of GVHD (or, in the case of solid organ transplantation, graft rejection), may outlast the period of administration of these agents; therefore, the duration of immunosuppressive therapy (which is used by many centres [20] to judge the duration of prophylaxis) may be an inappropriate discriminator to evaluate the best time to discontinue prophylaxis therapy. Whether antifungal chemoprophylaxis can be safely

discontinued with recovery of the CD4 T-lymphocytes or CD19 B-lymphocytes to greater than $0.2 \times 10^9/\text{L}$ and $0.1 \times 10^9/\text{L}$, respectively, is a question for further study.

Antifungal drug resistance

Triazole-based antifungal prophylaxis has resulted in a significant decline in invasive candidiasis [32,67–69,118]. Fluconazole prophylaxis has been associated in some cases with a selection for colonization by and breakthrough invasive infection due to less susceptible opportunistic yeast such as *Candida glabrata* and *C. krusei* [31,67,119–122]. Accordingly, it may be expected that prolonged prophylaxis targeting moulds such as *Aspergillus* spp. would permit the emergence of resistant fungi predicted by the weaknesses in the antifungal spectrum analogous to that for fluconazole. In one single-center retrospective experience, more than half of the patients who developed IMI due to non-*A. fumigatus* moulds had received antifungal prophylaxis with a parenteral polyene, suggesting a selection for more resistant pathogens [123]. Slowly sporulating variants of *A. fumigatus* have been associated with higher minimum inhibitory concentrations *in vitro* to a number of antifungal agents including itraconazole, voriconazole, and caspofungin [124]. The correlations between *in vitro* antifungal susceptibility profiles and clinical outcomes have not always been direct [125].

Clinical trials of empirical antifungal therapy and prophylaxis have been replete with examples of breakthrough fungal infections (defined by IFI documented during administration or within seven days of the antifungal agent [126]) due to organisms that might be expected to be susceptible to the administered agent. For example, while *in vitro* susceptibility studies might predict emergence of *A. terreus* [127] or *Scedosporium* spp. [128] infections among amphotericin B recipients, the breakthrough IFI reported among patients receiving amphotericin B-based regimens have included *Aspergillus* spp., *Fusarium* spp., *Geotrichum* spp., dematiaceous moulds, and *Candida* spp. [126,129,130]. A similar distribution of breakthrough IFI has been reported for itraconazole-based empirical antifungal therapy [129].

The spectrum of breakthrough IFI among empirical voriconazole therapy recipients has included some *Aspergillus* spp., *Candida* spp., and Zygomycete infections [131] but at rates lower than the comparators. Investigators in independent studies have reported breakthrough IFI due to non-albicans *Candida* spp. (*C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. guilliermondii*) and moulds including *Aspergillus* spp. and *Rhizopus* spp. among allogeneic HSCT recipients

receiving prophylactic itraconazole until day 100 to 180 post-transplant [5,132]. Indeed, recent reports of breakthrough IFI due to Zygomycetes occurring among HSCT patients receiving prophylactic or empirical voriconazole [133–135] provide a sobering reaffirmation of the observations of Walsh and colleagues [131]. These observations taken together with the known *in vitro* resistance profiles [136] predict that this group of moulds may limit the efficacy of long-term voriconazole-based prophylaxis strategies in high-risk HSCT recipients [137]. As noted earlier, these examples of clinical breakthrough IFI may not necessarily co-relate with *in vitro* antifungal susceptibility profiles [130] thus limiting the predictive value of such laboratory-based procedures. The evidence for the efficacy of extended-spectrum azoles such as itraconazole for the prevention of IMI in high-risk HSCT recipients, together with the widespread availability of voriconazole in the United States, may encourage even greater numbers of transplant physicians to prescribe prophylaxis over extended periods according to criteria as suggested in the survey by Trifilio *et al.* [20]. It seems likely that increasing use of long-term prophylaxis will be paralleled by further reports of breakthrough IFI.

Econotoxicity: how much is this all going to cost?

The prospect of funding the administration of the perfectly efficacious antifungal prophylaxis targeting moulds such as *Aspergillus* spp. over the course of 180 days of allogeneic HSCT-related immunosuppression seems daunting. In estimating the economic impact of preventing and treating IFI such as IA, considerations must include not only the drug costs, but also the hospitalization costs and the cost of post-hospitalization care among survivors. The estimated incremental cost for the treatment of invasive candidiasis and IA among transplant patients in the United States has been estimated to be as high as USD \$48,732 and \$86,635, respectively [138]. Using observed incidences of invasive yeast and mould infections in high-risk HSCT patients receiving or not receiving antifungal prophylaxis, estimated compliance with the prophylaxis regimen, non-fungal infection-related mortality, time to IFI, and time to death [5,67–69,132], together with drug costs estimated from the Red Book average wholesale price, estimates of the costs of treatment of IFI [138], and duration of prophylaxis of up to 180 days, an economic model can be developed to estimate the impact of chemoprophylaxis strategies using different agents [139–142].

For example, an extended-spectrum antifungal agent such as voriconazole, with both an oral and intravenous formulation effective for yeasts and moulds, when administered for prolonged antifungal prophylaxis in allogeneic HSCT with the expectation of similar compliance as for fluconazole in the same population, may cost approximately USD \$17,000 per patient compared to USD \$20,000 for fluconazole and USD \$23,000 for no antifungal prophylaxis. This represents an estimated saving of approximately USD \$3,000 to \$6,000 per patient. This assumes that the incidence of invasive candidiasis is approximately 3%, the incidence of invasive mould infection in the absence of prophylaxis is as for fluconazole recipients, approximately 15%, and the incidence of invasive mould infection among fully compliant voriconazole recipients would be similar to that for itraconazole, approximately 5% [5]. Of course, the value of such models lies in the accuracy and completeness of the assumptions used in the construction of the model.

One of the major assumptions, such as the incidence of invasive mould infection, may vary from center to center and from one group of patients to another. For example, if the above estimates were based on a 3% institutional incidence of invasive mould infection among the patient population of interest, the cost of voriconazole-based prophylaxis per patient could be approximately one-third higher than for fluconazole. Despite this, estimates for the highest-risk patients with expected incidences of invasive mould infection in the range of 15% suggest that long-term antifungal prophylaxis in target patient populations at highest risk may be cost-effective. Accordingly, an understanding of the local epidemiology of IFI in patients targeted for antifungal prophylaxis is critical to successful budgeting. Further large well-designed comparative clinical trials are needed to validate these estimates.

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