

Current Approaches in Antifungal Prophylaxis in High Risk Hematologic Malignancy and Hematopoietic Stem Cell Transplant Patients

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Abstract Invasive fungal infections (IFIs) pose the most serious infectious risk to patients with hematologic malignancies and in those undergoing hematopoietic stem cell transplantation (HSCT). Invasive candidiasis has an incidence of 8–18% and a mortality of 30–40% in various reports. Invasive aspergillosis has an incidence of 4–15% and an even higher mortality of 60–85% cited in the published literature. IFIs have remained difficult to diagnose in a timely way in neutropenic and immunocompromised patients. A timely diagnosis is essential in promptly initiating antifungal therapy in order to optimize clinical outcomes. Thus, antifungal prophylaxis has an enormous appeal to minimize the threat from IFIs. In this article, the epidemiology and risk factors for IFIs as well as evidence from antifungal prophylaxis clinical trials in certain patient groups with hematologic malignancies are reviewed. Antifungal prophylaxis has been shown to be effective in certain settings. However, concerns about shifts in fungal epidemiology, emergence of resistance, drug toxicities, and drug interactions must be considered in deciding how and in whom to use antifungal prophylaxis.

Keywords Antifungal prophylaxis · Hematological malignancies · Hematopoietic stem cell · Transplantation

Introduction

Invasive fungal infections (IFIs) pose the greatest life-threatening infectious threat during induction therapy for acute leukemia and during hematopoietic stem cell transplantation (HSCT). *Candida* and *Aspergillus* are the major fungal pathogens. Invasive candidiasis has an incidence of 8–18% with a mortality of 30–40% [1]. Invasive aspergillosis (IA) has an incidence of 4–15% with an even higher mortality rate of 60–85% [2]. The risk of developing IFIs has risen over the past 30 years [3].

Invasive fungal infections have remained difficult to diagnose in neutropenic patients. For example, 50% of patients with autopsy-proven invasive candidiasis did not have positive blood cultures prior to death [4]. The culture-based methods most commonly used today (Bactec Mycosis IC/F medium) can detect disseminated candidiasis in only 60% of cases within 2–5 days of incubation [4]. Respiratory secretions have poor yields for pulmonary aspergillosis and blood cultures are rarely positive in cases of hematogenous aspergillosis or Zygomycosis [4]. Tissue biopsies for histopathologic or culture-based diagnosis of visceral fungal infections, including pulmonary mold infections, are often challenging to obtain in this patient population group due to

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thrombocytopenia in many instances. High resolution-computed tomographic scans of the chest remain the most sensitive way to diagnose IA [5]. There have been advances in non-culture based methods of diagnosis such as the use of the double-sandwich enzyme-linked immunosorbent assay (ELISA) for serum galactomannan antigen, which is a major component of the cell wall of *Aspergillus* released during invasive infection, and beta-D-glucan which detects *Candida*, *Aspergillus*, and several other fungal genera [6, 7]. In a meta-analysis of proven or probable cases of IA, the sensitivity of the serum galactomannan antigen assay ranged from 61% to 71%, the specificity was 89–93%, the negative predictive value was 95–98%, and the positive predictive value was 26–53%. Therefore, the serum galactomannan assay has moderate sensitivity in confirming IA [6]. Beta-D-glucan is a cell wall component of many fungi, with notable exceptions of *Cryptococcus* and *Zygomycetes* species. The sensitivity and specificity of this test for the diagnosis of IFIs is 93% and 77%, respectively [7], but studies have been limited. The use of the polymerase chain reaction to detect fungi-specific deoxyribonucleic acid (DNA) and nucleic acid sequence-based amplification of fungal-specific messenger ribonucleic acid (mRNA) for the diagnosis of IFIs have not yet been defined. Therefore, despite the availability of two nonculture-based methods of diagnosis and others in development, there is difficulty in obtaining accurate and timely diagnosis of IFIs. Delays in promptly initiating antifungal therapy lead to suboptimal outcomes of infection. The presence of IFIs often causes delays in administering further anti-leukemic chemotherapy in many patients [8].

The difficulty in obtaining a timely diagnosis as well as the high morbidity and mortality associated with IFIs provide a rationale for consideration of antifungal prophylaxis. Nonetheless, primary antifungal prophylaxis remains a topic of some controversy with no clear consensus emerging amongst different centers. In this article, the epidemiology and risk factors for IFIs as well as evidence for the use of antifungal prophylaxis in patients with high risk hematologic malignancies and HSCT are reviewed.

Epidemiology and Risk Factors for IFIs

In patients with acute leukemia, the risk for *Candida* infections in published reports varies considerably.

Undoubtedly, this is related to the status of leukemia (newly diagnosed, post-remission, relapsed or refractory to treatment), duration of neutropenia, and the types of anti-neoplastic agents used in treatment.

Invasive fungal infections occur in a bimodal pattern after HSCT [9]. There is an early peak prior to engraftment. The intensive conditioning regimen results in profound neutropenia and mucosal injury, which are the major risk factors. The antibiotics used for management of neutropenic fever suppresses gut bacterial flora and allows fungal overgrowth. Most of the fungal infections during this early peak are due to *Candida*. The risk for *Candida* infections appears to be lower after less intensive conditioning regimens, so-called non-ablative transplants, due to a shorter duration of neutropenia and less mucosal injury. The types of lower intensity conditioning regimens vary considerably and there may be substantial differences that require further study.

The European Confederation of Medical Mycology conducted a survey of the rates of fungal infection in 106 centers between September 1997 and December 1999, with the participation of six national mycology societies (British, French, Germany, Italian, Spanish, and Swedish). The findings of the survey showed that for solid tumors, *Candida albicans* accounts for half of the cases of candidemia. However, in hematological malignancies, *C. albicans* is responsible for only 35% of cases of candidemia with the majority of cases being due to non-*albicans Candida* species such as *Candida tropicalis* (24%) and *Candida krusei* (12%) [10]. Prevention of *C. albicans*-related infections by fluconazole, commonly used in leukemic and HSCT patients, may account for this shift to less-azole-susceptible species of *Candida* [11]. In another study from Brazil conducted between 1997 and 2003, non-*albicans Candida* caused 78.9% of episodes of candidemia in patients with hematological malignancies and 51.6% in those with solid tumors ($P = 0.034$) [12].

The risk for IA in acute myelogenous leukemia patients ranges from 2% to 28% in the published literature with most series demonstrating rates in the range of 5–10% [13–20]. The risk varies considerably according to disease status. Patients with relapsed or refractory acute myelogenous leukemia undergoing salvage chemotherapy have the greatest risk, whereas newly diagnosed patients receiving induction chemotherapy have a lower risk and those in remission receiving consolidation therapy have the lowest risk.

For IA, duration of granulocytopenia is the major risk factor associated with the development of invasive pulmonary aspergillosis [21]. Invasive pulmonary aspergillosis developed at a rate of 1% per day early in the course of granulocytopenia and then at 4.3% per day between the 24th and 36th day [22]. The risk was low during the first 2 weeks of neutropenia, but increased substantially during the 3rd week and subsequently.

After allogeneic HSCT, the incidence of IA ranges between 4% and 24% [23–30]. One transplant center noted an increase over time, rising from 4% to 12% during the 1990s [29]. Another center noted a rate of 15% in the 1980s during a time where patients were transplanted in unfiltered rooms [31]; later, at the same institution, the rate was still 15% but there was a marked shift to later time of onset (92 days), during the period of GVHD and cytomegalovirus (CMV) infections [32]. On average, most centers report rates of IA of 11–15% in allogeneic HSCT patients. Rates of IA after autologous HSCT are much lower, generally 1–2% [33]. Recently, however, there have been reports of up to an 8% incidence of IA after autologous HSCT for patients with lymphoproliferative diseases (non-Hodgkin's lymphoma, Hodgkin's lymphoma, or multiple myeloma) who had been given immunosuppressive agents such as steroids, rituximab, fludarabine, or thalidomide in the 6 months prior to transplant [34].

Just as with *Candida*, the prophylactic use of anti-mold antifungal agents can account for the changing incidence patterns with molds. For example, there was a tripling of the incidence of IA over 15 years amongst recipients of allogeneic HSCT and less so after autologous HSCT at the Fred Hutchinson Cancer Research Center [35]. There was also an increase in *Fusarium* species and Zygomycetes, even though the absolute numbers of these infections remained low [35]. The emergence of non-*fumigatus Aspergillus* molds has been shown to be related to previous use of amphotericin B or azole antifungal agents [36]. The increase in the use of voriconazole prophylaxis has been associated with an increased frequency of Zygomycetes in some centers [37]. On the other hand, data collected prospectively in the TRANSNET consortium indicated that there were fewer than five cases of Zygomycetes per 1,000 transplants in 25 US transplant centers over a 3-year period during which voriconazole use was increasing and there was no trend for an increase over time [38].

Early onset of IA (40 days or less) occurs more commonly in those with prior infections by *Aspergillus* [39]. Among those with prior IA, several factors were associated with incremental increases in the risk of recurrence: <6 weeks of anti-*Aspergillus* therapy, advanced underlying disease, use of an ablative conditioning regimen, marrow or cord as the stem cell source, and the occurrence of CMV disease and GVHD after HSCT [39]. An additional risk factor for early IA is long pre-engraftment neutropenic periods such as that found in patients receiving umbilical cord stem cells transplants or those who fail to engraft [40].

Late-onset post-engraftment IA (41–180 days) is more common in patients transplanted for multiple myeloma and amongst those receiving peripheral blood stem cell transplants from mismatched or unrelated donors [2]. In addition, receipt of T-cell depleted or CD34-selected stem cell products, use of corticosteroids, neutropenia, lymphopenia, GVHD, CMV disease, and respiratory virus infections also increased post-engraftment IA. Very late-onset (more than 6 months after HSCT) IA has been associated with chronic GVHD and CMV disease [2].

Zygomycosis usually occurs more than 90 days after HSCT [35]. Risk factors for infection with Zygomycetes include underlying myelodysplastic syndrome and chronic GVHD and its therapy [35].

Clinical Trials of Anti-Fungal Prophylaxis in High Risk Hematologic Malignancy and HSCT Patients

Agents that may be considered for anti-*Candida* prophylaxis include the polyenes (amphotericin B, amphotericin B lipid formulations), triazoles (fluconazole, itraconazole, voriconazole, posaconazole), and the echinocandins (caspofungin, micafungin, anidulafungin). Agents that may be considered for anti-mold prophylaxis include the same agents, with the exception of fluconazole, which has no anti-mold activity.

Polyenes

Amphotericin B Deoxycholate

Low dose intravenous amphotericin B deoxycholate (0.1 mg kg⁻¹ day⁻¹) was effective in reducing the rate of proven systemic IFI compared to placebo

(8.8% vs. 14.3%) in autologous HSCT patients [41]. Prophylactic agent was significant in nephrotoxicity and infusion-related events [41].

Lipid Formulations of Amphotericin B

Lipid formulations of amphotericin B have been evaluated to take advantage of less systemic toxicity. Since amphotericin B remains in visceral tissues for a prolonged duration when administered as a lipid formulation, interrupted dosing is permissible. Several studies have evaluated weekly administration. Liposomal amphotericin B infusions administered at a dose of 10 mg kg⁻¹ weekly for 8 weeks was given to eight allogeneic HSCT patients after ablative conditioning; significant adverse events (dyspnea, chest pain, abdominal pain, tubulointerstitial nephritis, renal insufficiency, anuria, and anaphylactic shock) were noted and led to the discontinuation of the liposomal amphotericin B in 100% of the patients [42]. Similarly, when 21 patients being treated with high dose prednisone (2 mg kg⁻¹day⁻¹) for acute GVHD, after reduced intensity-conditioned allogeneic HSCT were given prophylactic liposomal amphotericin B infusions, 33% of the patients discontinued liposomal amphotericin B due to drug-related adverse events, consisting of elevated serum creatinine above 1.5 times the baseline in five patients, hypotension in another patient, and violent chest pain and arrhythmia in another patient [43]. Amphotericin B lipid complex (4 mg kg⁻¹ twice weekly infusions) given to 63 adult allogeneic HSCT patients from day+30 onwards while they were receiving 30 mg day⁻¹ or more of prednisone, resulted in a median creatinine increase of 0.85 mg dl⁻¹ [44]. Thus, even though this approach may hold promise, the optimal dose schedule has not been established and efficacy has not been demonstrated as yet.

Aerosolized Amphotericin B Formulations

The initial process in the pathogenesis of invasive pulmonary aspergillosis is inhalation of *Aspergillus* conidia. Aerosolized amphotericin B delivers topical antifungal therapy to the lungs to prevent invasive pulmonary aspergillosis and also circumvents the systemic toxicities and drug–drug interactions associated with intravenous systemic amphotericin B. Another advantage of the use of aerosolized amphotericin B is that due to a lack of systemic absorption of

this agent, the sensitivity of the serum galactomannan assay in the early diagnosis of invasive pulmonary aspergillosis is preserved (although it still may affect BAL galactomannan values) [45].

In a prospective randomized controlled trial, aerosolized amphotericin B deoxycholate did not reduce the incidence of invasive pulmonary aspergillosis [46]. This may be due to the deoxycholate component of conventional amphotericin B, which impairs the surface tension lowering function of pulmonary surfactant [47]. Pulmonary surfactant-like function is, however, retained by the phospholipids and cholesterol which serve as the liposomal carriers of amphotericin B [48].

Prophylactic aerosolized amphotericin B lipid complex given once daily for 4 days and then once weekly for 13 weeks to allogeneic HSCT patients until day 100 along with standard fluconazole prophylaxis, resulted in a 20% or more decrease in pulmonary function, specifically the forced expiratory volume in 1 s and forced vital capacity, in 5% of patients [49]. No patients were withdrawn from this study. Only 1 of 40 patients developed an IFI with fusariosis [49]. This was a non-comparative trial.

In a placebo-controlled trial, aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis was given prophylactically twice a week during the prolonged neutropenia seen after chemotherapy administration for hematologic malignancies or during HSCT (autologous and allogeneic) until the neutrophil counts increased to more than 300 cells per mm³ [50]. In addition, all patients received prophylactic fluconazole as standard of care. The doses of fluconazole used were not delineated specifically in the article. On the intent to treat analysis, 18 of 132 patients receiving placebo-developed invasive pulmonary aspergillosis in comparison to 6 of 139 patients in the liposomal amphotericin B group ($P = 0.005$). Toxic effects from aerosolized liposomal amphotericin B were tolerable (mostly related to the inhalation). There were no systemic toxicities noted. The creatinine level remained at the baseline during liposomal amphotericin B administration. The major side effect was coughing which required temporary discontinuation of therapy for 1 week in 45% of the aerosolized liposomal amphotericin B group and in 30% of the aerosolized placebo group ($P = 0.01$). Data on pulmonary function tests were not reported in this study which could be

important to fully understand the ramifications of aerosolized liposomal amphotericin B therapy, especially for patients with lung GVHD after HSCT. The study was not designed to evaluate invasive pulmonary aspergillosis-related mortality or overall mortality. Aerosolized liposomal amphotericin B appears to be a promising agent to reduce the risk of invasive pulmonary aspergillosis in immunocompromised patients, but more data are needed on its impact on pulmonary function tests, invasive pulmonary aspergillosis-related mortality and overall mortality.

Fluconazole and Itraconazole

Fluconazole prophylaxis, in two prospective randomized trials conducted in autologous and allogeneic HSCT patients, has been demonstrated to reduce IFIs due to yeasts prior to engraftment. In a double-blind randomized multicenter trial, hematopoietic stem cell transplant recipients (52% allografts and 48% autografts) were randomly assigned to receive prophylactic fluconazole 400 mg daily or placebo from the start of conditioning until the neutrophil count increased to $1,000 \text{ ml}^{-1}$, systemic fungal infection developed or there was excessive toxicity, whichever came first [25]. Systemic fungal infection occurred in 15.8% of those who received placebo versus only 2.8% of patients receiving fluconazole and this was statistically significant ($P < 0.001$). All species of *Candida* except *Candida krusei* were prevented by fluconazole. There was a statistically significant reduction in infection-related mortality (16 deaths out of 177 patients on the placebo arm vs. 1 death out of 179 patients in the fluconazole group, $P < 0.001$), although there was no reduction in the overall mortality. Fluconazole was well-tolerated save for a higher mean increase in serum alanine aminotransferase [25].

In another randomized, double-blind placebo-controlled trial, patients were given either fluconazole 400 mg daily during the first 75 days after bone marrow transplantation (88% allografts and 12% autografts) or placebo [23]. Systemic fungal infection (7% vs. 18%, $P = 0.004$), infection-related mortality (12% vs. 22%), and overall mortality (20% vs. 35%, $P = 0.004$) were significantly reduced in the fluconazole-treated patients versus those given placebo [23]. A recent analysis of long-term outcomes of these patients showed continuing benefit beyond the course of fluconazole prophylaxis with a further benefit in survival [24].

Fluconazole prophylaxis was found to be an independent predictor for overall survival in a multivariate analysis of factors associated with survival after matched unrelated donor transplants [51]. In a meta-analysis involving 16 trials evaluating fluconazole prophylaxis versus placebo in neutropenic patients by Kanda et al., only fluconazole doses at 400 mg a day were associated with reduced risk of IFI and fungal-related death and only if the incidence of systemic fungal infection at the center was more than 15%, seen mainly in hematopoietic stem cell transplant patients [52]. As expected, no reduction in *Aspergillus* infection and non-*albicans Candida* species was found with the use of fluconazole. One randomized trial evaluated fluconazole at 200 mg day^{-1} and found it to be as effective as 400 mg day^{-1} [53].

The risk for *Candida* infections in acute leukemia therapy and after autologous HSCT is lower and somewhat heterogeneous [15, 16, 54]. Accordingly, trials evaluating fluconazole prophylaxis in such patient populations have provided varied results. To determine whether there is a role for anti-yeast prophylaxis in all acute leukemia and HSCT patients, Kanda's meta-analysis of fluconazole prophylaxis trials found that a benefit against *Candida* was discernible if the incidence of systemic fungal infection was more than 15% and this was seen mainly in allogeneic HSCT patients [52].

Overall, fluconazole prophylaxis has been found to be safe and effective and is now widely used in HSCT centers and consensus guidelines support its routine use after allogeneic HSCT [55]. Issues that remain unresolved about fluconazole prophylaxis are the optimal duration of prophylaxis (halting at the time of engraftment or continuation until the risk of GVHD has abated), whether all acute leukemic patients should receive prophylaxis, and its role in autologous transplant patients, non-ablative transplant recipients, and in those with acute or chronic GVHD.

Itraconazole has been extensively studied as anti-fungal prophylaxis in cancer patients. Most of these trials found itraconazole to have similar efficacy to fluconazole in the prevention of *Candida* infections. However, several shortcomings of the various trials prevented a clear determination as to whether there was protection against IA: the risk for *Aspergillus* infections was too low in the patients studied, there were differences in itraconazole formulations used,

and the sample sizes of the studies in patients with hematologic malignancies were not large enough to determine if there was any protection against IA. To assess the *Aspergillus* question more fully, Glasmacher performed a meta-analysis of neutropenic patients with hematological malignancies and patients after allogeneic stem cell transplantation receiving antifungal prophylaxis with itraconazole, fluconazole, or amphotericin B [56]. Patients receiving itraconazole had a lower risk for IFIs of all types and reduced mortality from fungal infections. Recognizing that the oral solution of itraconazole had greater bioavailability than the oral capsules, studies using oral solution (at a dose of 400 mg day⁻¹) were examined separately. The rate of *Aspergillus* infections in patients receiving the oral solution of itraconazole was reduced by 48%.

Itraconazole was compared to fluconazole in two randomized trials as long-term antifungal prophylaxis (up to day+100 or day+180) after allogeneic HSCT [57, 58]. In one trial (by Winston and colleagues), fewer IFIs occurred in the itraconazole arm (9% vs. 25%, $P = 0.02$), but there was no impact on overall survival [57]. More patients in the itraconazole arm than the fluconazole arm had the study drug discontinued due to death (30% vs. 18%, $P < 0.05$) or adverse events (8% vs. 1%). Itraconazole failures tended to occur mainly in those with inadequate drug levels.

In the second trial, by Marr et al., higher doses of itraconazole were used to ensure therapeutic drug levels and doses were adjusted [58]. There was no reduction in the IFI rate in the itraconazole group and the overall survival was similar in each group. More renal and hepatic toxicities were noted in patients receiving itraconazole. A higher mortality rate in the itraconazole group led to premature closure of this trial [58]. In those who were actually able to tolerate itraconazole and remain on itraconazole, there were fewer IFIs (7% during itraconazole exposure in comparison to 15% on the fluconazole arm, $P = 0.03$).

These two trials suggest a lack of substantial advantage (over fluconazole) for itraconazole prophylaxis, with concerns for both safety and efficacy as long-term anti-*Aspergillus* prophylaxis in allogeneic HSCT recipients. Other studies have raised concerns that itraconazole may not offer greater protection than fluconazole [20, 59, 60]. Even though itraconazole has activity against *Aspergillus*, bioavailability is

suboptimal, variable, and there is high inter-patient variability. There may be poor tolerability of the cyclodextrin containing oral solution in patients with mucositis and erratic bioavailability of the oral capsule formulation of itraconazole [61]. Furthermore, itraconazole is cardiotoxic with negative inotropic effects and can cause interactions with concomitant administration of high dose cyclophosphamide, vincristine, and perhaps other hepatically metabolized drugs such as anthracyclines. The concomitant use of itraconazole with chemotherapy drugs metabolized by cytochrome P450 isoenzymes may lead to potentially harmful drug interactions with resultant greater toxicity of the chemotherapy [62].

Furthermore, in a meta-analysis of itraconazole prophylaxis in neutropenic patients treated for hematologic malignancies, only the itraconazole solution and not the capsules reduced the incidence of IA due to a higher bioavailable dose of itraconazole [56]. Tolerability of itraconazole is also problematic as shown in the trial by Winston et al., where more itraconazole-treated patients discontinued therapy than the fluconazole arm of the study [57]. Itraconazole failures were seen mainly in those with inadequate drug levels and these patients had a lower fungal-free survival. In the trial by Marr et al., higher doses of itraconazole were used to ensure adequate drug levels but at the expense of excess renal and hepatic toxicity from itraconazole [58].

Echinocandins

The efficacy of an echinocandin (micafungin) for antifungal prophylaxis in neutropenic patients undergoing HSCT was demonstrated in a randomized trial [64]. Either micafungin 50 mg intravenously daily or fluconazole 400 mg intravenously once a day was given from the start of conditioning to 5 days after engraftment. Success was defined as the absence of suspected, proven or probable IFI through the end of therapy and the absence of a proven or probable IFI in the 4-week period after treatment. Micafungin was successful in 80% of patients and fluconazole was successful in 73.5% of patients ($P = 0.03$). Micafungin also reduced the need for empiric anti-fungal therapy and was at least as safe a fluconazole therapy. Both study drugs were equally effective in preventing candidiasis but there was a non-significant trend to fewer episodes of aspergillosis in the micafungin arm

(0.2% vs. 1.5%, $P = 0.07$). There was no difference in overall mortality.

In a randomized comparative trial, caspofungin and itraconazole prophylaxis given to patients with hematologic malignancies in a single-center trial were compared [65]. Both groups had the same rates of IFI and mortality [65].

These studies indicate that the echinocandins are effective in *Candida* prevention. The echinocandins offer an advantage over fluconazole in the greater spectrum of activity across the various *Candida* species, covering *C. krusei* and *C. glabrata*, which are not reliably covered by fluconazole, and they should be considered in centers that have a substantial risk for invasive infection by these *Candida* species. Another potential advantage is anti-*Aspergillus* activity; unfortunately, no clinical trial to date has demonstrated that *Aspergillus* infections are prevented with a clinically meaningful benefit. The major draw-back of the echinocandins is the need for intravenous administration, making its use in long-term antifungal prophylaxis challenging, and at a substantially greater cost.

Extended Spectrum Azoles

Posaconazole is an extended spectrum oral azole with a wide range of activity against *Candida* species, *Aspergillus*, *Fusarium*, and Zygomycetes, with an acceptable adverse event profile. In a randomized open-label study of patients with high risk neutropenia from chemotherapy given for acute myelogenous leukemia or myelodysplastic syndrome, the safety and efficacy of posaconazole prophylaxis was compared to that of fluconazole or itraconazole [20]. Prophylaxis was given with each cycle of chemotherapy until resolution of the neutropenia and complete remission, until development of IFI, or for up to 12 weeks, whichever came first. The incidence of proven or probable IFI was significantly lower in the posaconazole compared to the fluconazole or itraconazole arm (2% vs. 8%, $P < 0.001$). This reduction in IFIs persisted for 100 days with posaconazole (5% vs. 11%, $P = 0.003$). Fewer cases of *Aspergillus* infection developed in patients given posaconazole versus fluconazole or itraconazole (1% vs. 7%, $P < 0.001$). In the Kaplan–Meier analysis of the time to death from any cause at the end of the 100-day period, there was an improvement in overall survival in the

posaconazole arm ($P = 0.004$). There was a 33% relative reduction in mortality after 100 days in the posaconazole arm. However, serious adverse events, possibly or probably related to treatment, were reported in 6% of the posaconazole arm and in 2% of the fluconazole or itraconazole arm ($P = 0.01$). What is not clear from the study is whether or not there may have been a deleterious interaction of posaconazole with the chemotherapy. Since more than 40% of patients received more than one course of chemotherapy, the question is raised if the excess toxicities in the posaconazole group occurred more frequently in patients receiving concomitant chemotherapy? This concern is important in view of the demonstrated harmful interactions of itraconazole with certain chemotherapy agents noted above. Posaconazole is structurally similar to itraconazole but with fluorine substituents in place of chlorine and a furan ring in place of the dioxolane ring [63]. Posaconazole has a similar drug interaction profile to itraconazole since posaconazole is a substrate for the CYP450 enzymes and thereby interactions are expected with drugs that are metabolized via CYP3A4 [63].

Invasive fungal infection rates as high as 39% have been reported in patients with extensive chronic GVHD, mainly from IA [21]. Most of the previous trials administered antifungal prophylaxis during the first 100 days after HSCT [23–25, 57, 64]. In a randomized double-blind trial, the efficacy of oral posaconazole was compared to oral fluconazole for IFI prophylaxis in patients with GVHD receiving immunosuppressive therapy [66]. The primary endpoint was the IFI incidence from randomization to day 112 after the first dose of the study drug. At the end of the 112-day treatment period, posaconazole was found to be as effective as fluconazole in preventing IFIs (5.3% vs. 9%, $P = 0.07$) and was better than fluconazole in preventing proven or probable aspergillosis (2.3% vs. 7%, $P = 0.006$), reflecting the lack of efficacy of fluconazole against molds which are the major fungal pathogens seen in GVHD. During the exposure period, there were fewer breakthrough IFIs in the posaconazole arm (1% vs. 5.9%, $P = 0.001$). Overall mortality was similar in the two groups, but the mortality attributable to IFIs was lower in the posaconazole group (1% vs. 4%, $P = 0.046$). Baseline serum galactomannan assays were performed at entry into the study. Patients with baseline serum galactomannan

antigen positivity had a higher likelihood of developing IFIs on either the posaconazole or fluconazole arm (2/21 or 10% vs. 7/30 or 23%), than those cases without serum galactomannan positivity at baseline (12/259 or 5% vs. 20/243 or 8%) [66]. The antifungal effect was present only in patients with baseline positive serum galactomannans, suggesting that such patients were already infected at baseline. This raises questions about whether this really was a prophylactic effect or not: were these really treatment of incipient *Aspergillus* infections rather than prevention? Also important to note is that the benefit of anti-mold prophylaxis was attenuated by the administration of intensive immunosuppression for GVHD therapy. For example, if methylprednisolone was given at a dose of 2 mg kg⁻¹ day⁻¹ or greater, the risk for IFI was still 10% on the posaconazole arm. In the analysis of this trial performed by the United States Food and Drug Administration (Noxafil package insert) in which a composite endpoint of clinical failure (IFI, death, use of systemic antifungal therapy) was used, clinical failures occurred in 33% of patients given posaconazole and 37% of patients given fluconazole and these differences were not statistically different. The discontinuation rate in the posaconazole and fluconazole arms in this trial was the same indicating posaconazole to be as well tolerated as fluconazole.

Voriconazole is a well-tolerated triazole, with broad spectrum antifungal activity, and is available in oral and intravenous formulations [67]. The Bone Marrow Transplant Clinical Trials Network (BMT CTN) in the United States performed a multicenter, randomized double-blind trial of extended prophylaxis with either voriconazole 200 mg twice a day given either by mouth or intravenously versus fluconazole 400 mg a day, also administered either by mouth or intravenously after myeloablative allogeneic HSCT and the preliminary analysis was recently presented [68]. The study drug was given for 100 days (or 180 days in those patients on corticosteroids at a threshold dose of 1 mg kg⁻¹day⁻¹ or in those who received a T-cell depleted stem cell graft and whose CD4 count was less than 200 µl⁻¹ at day 100). The primary objective of the study was to compare the fungal-free survival rates between the two study arms through day 180. The secondary objectives included the comparison of the frequency of IFI, time to IFI, and the survival rate. Intensive galactomannan screening was done twice weekly for 60 days and then once weekly until

day+100 if there was no GVHD or continued at twice weekly if there was GVHD. Serum galactomannan positivity triggered intensive evaluation to document IFI. Standardized empirical antifungal therapy was permitted for suspected IFI, limited to <14 days. The total number of IFIs (proven, probable, or presumptive) were similar in the two groups at 6 months (10.5% for fluconazole and 6.6% for voriconazole, $P = 0.11$). Microbiologically documented proven or probable IFIs at 6 months in the fluconazole or voriconazole arm were caused by *Aspergillus* (16 cases vs. 7 cases, $P = 0.05$), *Candida* (three cases in each arm), and Zygomycetes (three cases in the fluconazole arm and two cases in the voriconazole arm) and this is statistically not significant. The total number of microbiologically documented IFIs at 6 months was not statistically significant in either the fluconazole or voriconazole arm (23 vs. 13, $P = 0.11$). The fungal-free survival rates and overall survival were similar in both arms at 6 and 12 months. The rates of adverse events and premature study drug withdrawal were similar for both arms of the study.

These trials suggest a benefit to using extended spectrum azoles as primary antifungal prophylaxis [20, 66] (Table 1). However, even though the oral formulations of the extended spectrum azoles allow prolonged use to cover longer risk periods, oral azoles have variable bioavailability. Voriconazole levels in patients receiving oral drug have been found to be variable after HSCT [69, 70]. Voriconazole is metabolized in the liver via the cytochrome P450 pathway, chiefly by the CYP2C19 isoenzyme which exhibits genetic polymorphism resulting in reduced metabolism in 15–20% Asians, 3–5% Caucasians and African Americans [69]. Voriconazole over and under exposure resulting from variable blood levels have clinical implications [70]. An increase in voriconazole levels has been associated with hepatotoxicity [69, 70]. Toxic encephalopathy was seen in a patient with an increase in the voriconazole area under the concentration-time curve (AUC). A low voriconazole AUC was found in a patient with persistent signs of IA [68] (Tables 2 and 3).

Variable levels of posaconazole have been noted in patients receiving salvage therapy for Aspergillosis [71]. Higher plasma concentrations of posaconazole were associated with greater response rates [71]. For example, an average plasma concentration in the lowest quartile had a response rate in IA of 24% in

Table 1 Clinical trials of antifungal prophylaxis with azoles

Trial	Population	Agent	IFI	IA	Fungal-related mortality	OS	AE
Goodman [25]	HSCT	Fluconazole	2.8% ^a	NR	1 in 179 patients ^a	NS	Increase ALT
		Placebo	15.8% ^a	NR	16 in 177 patients ^a	NS	None
Slavin [23]	HSCT	Fluconazole	7% ^a	NR	12% ^a	20% ^a	NS
		Placebo	18% ^a	NR	22% ^a	35% ^a	NS
Winston [57]	HSCT	Itraconazole	9% ^a	4%	9%	NS	More GI symptoms
		Fluconazole	25% ^a	8%	18%	NS	NS
Marr [58]	HSCT	Itraconazole	13%	5% ^a	NS	NS	More GI, hepatic and renal toxicity
		Fluconazole	16%	12% ^a	NS	NS	NS
Cornely [20]	AML/MDS	Posaconazole	2% ^a	1% ^a	2% ^a	16% ^a	NS
		Fluconazole or Itraconazole	8% ^a	7% ^a	5% ^a	22% ^a	NS
Ullmann [66]	HSCT/GVHD	Posaconazole	5% ^a	2% ^a	1% ^a	NS	NS
		Fluconazole	9% ^a	7% ^a	4% ^a	NS	NS
Wingard [68]	HSCT	Voriconazole	NS	7 cases	NS	NS	NS
		Fluconazole	NS	16 cases	NS	NS	NS

HSCT hematopoietic stem cell transplants, AML acute myelogenous leukemia, MDS Myelodysplastic syndrome, NS not statistically significant, GI gastrointestinal, ALT serum alanine aminotransferase, GVHD graft-versus-host disease

^a Reached statistical significance

Table 2 Acceptable antifungal agents for use as prophylaxis in acute myelogenous leukemia

Induction therapy	Post-remission consolidation therapy
Fluconazole	Not studied
Posaconazole	
Itraconazole	

comparison to a 75% response rate in those with an average plasma concentration of posaconazole in the highest quartile [71]. This further highlights that posaconazole should be taken with a high fat meal to allow for optimal absorption. A recent study noted low blood levels in HSCT patients with diarrhea [72]. Even with the use of posaconazole prophylaxis, there can be IFI failure rates. The posaconazole package insert states that HSCT patients with GVHD have a 33% IFI failure rate and those with acute myelogenous leukemia have a 52% IFI failure rate. Therefore, the use of extended spectrum azoles does not eliminate the concern about IFIs.

One important consideration is the lack of anti-Zygomycetes activity by voriconazole. As noted earlier, the TRANSNET study did not show a trend to increased Zygomycosis over time as voriconazole

came into use [38]. Both posaconazole trials had only two cases of Zygomycetes in a combined 600 patients in the fluconazole arm [20, 66]. The BMTCTN trial had five cases of Zygomycetes in 600 patients with no difference between the voriconazole or fluconazole arm [68]. Therefore, although the concern about increases in Zygomycetes infections in recent years has been raised and several single-center studies suggest the growing use of voriconazole may contribute to the rise in Zygomycetes infections, the data from prospective multi-center trials suggest that the threat remains quite low. These data suggest that at present, the concern about Zygomycetes should not drive the decision to use extended spectrum azoles for antifungal prophylaxis, except in those centers which have high rates of Zygomycosis.

Conclusions

Antifungal prophylaxis can be highly effective in reducing the morbidity and mortality of IFIs. Multiple controlled clinical trials have provided important insights as to the effectiveness of antifungal prophylaxis. Fluconazole prophylaxis has been widely

Table 3 Acceptable antifungal agents for use as prophylaxis in autologous HSCT and allogeneic HSCT

Pre-engraftment (prior to neutrophil recovery)	Post-engraftment
Autologous HSCT	
Fluconazole	None
Allogeneic HSCT	
Fluconazole	Fluconazole
Itraconazole	Itraconazole
Posaconazole	Posaconazole ^a
Micafungin	Voriconazole
Voriconazole	
Aerosolized liposomal amphotericin B	

^a During GVHD requiring systemic corticosteroid therapy

accepted as the standard of care for prevention of *Candida* infections in the HSCT setting. The role for *Candida* prophylaxis in acute leukemia patients remains less clear due to variable rates of infections in different series. For the prevention of *Aspergillus* infections, several recent trials suggest benefit in acute leukemia and allogeneic HSCT patients using extended spectrum azoles. However, due to the heterogeneity of risk for IFIs in different patient groups, anti-*Aspergillus* prophylaxis may be appropriate in some groups but not clear in other patient populations. Further study is needed to better define which patient groups are at greatest risk for developing *Aspergillus* infections, in order to target those at greatest need for prophylaxis so as to optimize survival. A better understanding is required of the determinants of drug bioavailability to ensure adequate blood levels of the oral azoles. Additional data are needed to determine whether interactions between the extended spectrum azoles occur between various hepatically metabolized chemotherapy drugs, and if so, what adjustments are needed to allow these to be given safely.

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