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Review Article

ANTIFUNGAL PROPHYLAXIS IN AML INDUCTION THERAPY

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ABSTRACT

Patients receiving induction therapy for AML are at high risk for developing invasive fungal infections (IFIs). IFIs are significant as they are associated with substantial morbidity, delayed cancer treatment, increased health services utilization, and treatment-related mortality. Intensive chemotherapy destroys the mucosal barrier, leading to mucositis, colitis, or gastritis, which predisposes patients to systemic fungal propagation and/or fungemia. Early diagnosis and treatment improve patient's outcomes. However, establishing the diagnosis of systemic fungal infections is difficult as they do not manifest with specific symptoms or signs, blood cultures are often negative, and obtaining the tissue for histologic examination is difficult. Up to one-fourth of patients develop IFI during induction therapy of AML with an associated mortality of 40%-60%. Infections with Candida and *Aspergillus* species are most common. Systemic antifungal prophylaxis (AFP) is an effective approach to reducing the incidence of IFI. Comprehensive knowledge of antifungal agents, their activity, efficacy, and resistance patterns is required for designing effective AFP strategies. This review addresses the evidence on the prophylactic role of various available antifungal agents, their efficacy, and duration of therapy with a brief note on recommendations.

BACKGROUND

Invasive fungal infections are common in high-risk patients with hematologic malignancies, such as patients with acute leukemia receiving induction chemotherapy, and cause substantial morbidity and mortality. The duration and severity of neutropenia, prolonged antibiotic use, and the number of chemotherapy cycles increase the risk of invasive fungal infections. The rising incidence of life-threatening invasive fungal infections (IFIs) among cancer patients, the difficulty in establishing the diagnosis early in the course of infection, and the recognition that treatment outcomes are poor if initiation of therapy is delayed, prompted the interest in antifungal prophylaxis (AFP) for high-risk patients receiving chemotherapy [1]. The duration of neutropenia in leukemic patients is frequently more than 21 days. The major cause of morbidity and mortality during induction chemotherapy in patients with acute myeloid leukemia (AML) are IFIs which are caused by both yeasts and molds [2].

EPIDEMIOLOGY

Before the usage of AFP, the majority of fungal infections that occurred during neutropenia are caused by Candida, followed by *Aspergillus* [3]. More recently, Candida has been surpassed by *Aspergillus* as a cause of IFI in these patients, likely because of the use of AFP targeting Candida [4-6]. There is a substantial risk of mortality with both pathogens. Nonspecific clinical symptoms and/or signs, equivocal imaging results, and inadequate specimen sampling hamper early diagnosis. Often conventional microbiological tests fail to make an early or accurate diagnosis of IFI, and histological tests are difficult to perform in such patients. The toxicity and efficacy of antifungal agents also hinder the appropriate treatment of the disease [7].Given this, AFP is recommended in patients with AML undergoing induction therapy.

Candida Infection

The incidence of invasive *candidiasis* varies with the duration of neutropenia, the types of antineoplastic agents used and the underlying disease (newly diagnosed, in remission, relapsed, or refractory to treatment). Rates of invasive Candida infection in patients with hematologic malignancies not receiving antifungal prophylaxis have ranged from 8 to 24% [8]. The most frequent clinical manifestation of invasive *candidiasis* is *candidemia* and it is also a common fungal cause of central venous catheter-associated infections. Chronic disseminated *candidiasis* occurs less commonly. The most common species that accounts for about half of invasive Candida infections is *Candida albicans*. Patients with AML are also at increased risk for infections caused by non-albicans Candida species. Wingard *et al* assessed the frequency and distribution of non-albicans Candida species which accounted for 46% of all

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systemic *candida* infections, *Candida tropicalis* accounted for 25%, Candida glabrata for 8%, Candida parapsilosis for 7%, and Candida krusei for 4% [9].

Mold Infection

Aspergillus is the most common mold pathogen in patients causing IFIs with the incidence of invasive *Aspergillosis* (IA) ranging from 2 to 28% [8]. The most common *Aspergillus* species to cause disease is *Aspergillus fumigatus*, but several other *Aspergillus* species also cause invasive disease. Newly diagnosed AML patients receiving induction chemotherapy are at lower risk as compared to relapsed or refractory AML patients receiving salvage chemotherapy. AML patients in remission who are receiving consolidation chemotherapy are at the lowest risk. Inhalation into the sinuses and respiratory tract is the usual portal of entry of this airborne organism, with pneumonia being the most frequent manifestation of invasive *Aspergillosis*. Clinical manifestations can include the spectrum from the involvement of lungs with pulmonary infiltrates typically consisting of one or more nodules with or without surrounding ground-glass opacities (the halo sign), cavities, air-crescent signs, or focal airspace consolidation to the other manifestations such as sinusitis, localized skin ulcers, subcutaneous nodules, cerebral infarction, and/or fulminant disseminated disease. The second most common cause of mold infections are the agents of mucormycosis and can cause life-threatening rhino-orbital, pulmonary, cerebral, and/or disseminated infection. *Fusarium* and *Scedosporium* have also been reported. Infections with endemic fungi (*histoplasmosis, blastomycosis,* and coccidioidomycosis) are uncommon and the major risk factors are prolonged glucocorticoid use or other immunosuppression who have lived in or traveled to endemic areas [10].

PRIMARY PROPHYLAXIS

Multiple studies demonstrated the benefit of primary prophylaxis which involves the administration of an antimicrobial agent to prevent infection in patients at increased risk and who have not previously had the type of infection being targeted. Much of the emphasis historically has been on the prevention of Candida infections. Prophylaxis with an orally administered antifungal agent remains an attractive strategy because of ease of administration, compliance, and lack of toxicity. Various studies evaluating the efficacy of antifungal prophylaxis are shown in table I.

Fluconazole

Fluconazole is one of the recommended anti-fungal prophylactic agents in patients receiving induction therapy for AML and transplant recipients. It is a triazole antifungal agent with activity against many common fungal pathogens causing infection in patients with acute leukemia. It has a favorable pharmacokinetic profile that includes a long serum half-life, making once-daily administration possible, more consistent absorption from the gastrointestinal tract, excellent penetration into the cerebrospinal fluid, and elimination predominantly by renal mechanisms.

It has the advantage of being available as both oral and intravenous formulations with excellent tolerability, inexpensive generic formulations, and less severe drug interactions compared with the extended-spectrum azoles. The disadvantages include the spectrum of activity against Candida species is narrower than the echinocandins and breakthrough infections with fluconazole-resistant Candida species, especially C. krusei and *C. glabrata*, have been reported and have no activity against *Aspergillus* or other molds in comparison with the other acceptable agents.

Rotstein *et al* conducted a randomized, double-blind trial comparing oral fluconazole (400 mg daily) with placebo as prophylaxis for adult patients receiving intensive cytotoxic therapy for acute leukemia or autologous bone marrow transplantation. They had included 304 patients and reported that the usage of fluconazole resulted in fewer superficial fungal infections (7% vs. 18%; p 0.02) and fewer definite and probable IFI (6% vs. 24%; p 0.0001). Fluconazole prophylaxis did not obviate the need for parenteral antifungal therapy compared with placebo (57% vs. 50%). Fluconazole recipients had fewer deaths attributable to definite IFI (6.7% vs. 40%; p 0.04). Patients with AML who were undergoing induction therapy with cytarabine plus anthracycline-based regimens and those receiving marrow autografts not supported with hematopoietic growth factors are the most benefitted from fluconazole prophylaxis. They concluded that fluconazole prophylaxis reduces the incidence of superficial fungal infection and IFI and fungal infection-related mortality among patients who are receiving intensive cytotoxic chemotherapy for remission induction [11].

Winston *et al* did a double-blind, placebo-controlled trial of prophylactic fluconazole in neutropenic patients undergoing chemotherapy for acute leukemia. Patients were randomly assigned to receive either fluconazole (400 mg orally once daily or 200 mg intravenously every 12 hours) or placebo. Fluconazole decreased fungal colonization (29% vs 68%, $p< 0.001$) and proven fungal infections (9% vs 21%, $p = 0.02$). Fluconazole reduced the incidence of superficial fungal infections (6% vs 15% $p = 0.01$), and invasive fungal infections (4% vs 8% $p= 0.3$) and was especially effective in eliminating colonization and infection by Candida species other than Candida krusei. Aspergillus infections were infrequent in both groups. The use of amphotericin B, the incidence of drug-related side effects, and overall mortality were similar in both study groups. Fluconazole could not be clearly shown to be effective for preventing invasive fungal infections, reducing the use of amphotericin B, or decreasing the number of deaths [12].

Voriconazole

Voriconazole, a triazole antifungal agent, is available as a lyophilized powder for solution for intravenous infusion, film-coated tablets for oral administration, and powder for oral suspension. The pharmacokinetics is non-linear due to the saturation of its metabolism and with high inter individual variability. It is active against most strains of the following microorganisms, both in vitro and in clinical infections such as *Aspergillus fumigatus Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Fusarium solani*, *Scedosporium apiospermum.*Shah *et al* conducted a study to evaluate the role of Voriconazole as an antifungal prophylactic agent during induction therapy in AML. They had reported 6.6% incidence rates of proven/probable/possible (ppp) IFI. Voriconazole (when compared to fluconazole) had reduced the incidence of pppIFI (5/75, 6.6% vs. 19/66 29%; $P < 0.001$), need to start therapeutic (empiric + pppIFI) antifungals (26/75 34% vs. 51/66, 48%; $P < 0.001$) and delayed the start of therapeutic antifungals in

those who needed it (day 16 vs. day 10; P <0.001). Mortality due to IFI was also reduced with the use of voriconazole (1/75, 1.3% vs. 6/66, 9%; P = 0.0507), but this was not significant [13].

Oral voriconazole seems to be comparable with AmB with less toxicity and more convenience. Mandhaniya *et al* compared the efficacy and toxicity of Amphotericin B(AmB) and voriconazole as AFP in pediatric acute leukemia patients. Failure of prophylaxis occurred in 14/50 patients in the voriconazole arm (1 proven mucormycosis, 1 possible IFI, 11 empirical antifungal therapy, and 1 withdrawal owing to hepatotoxicity) and 17/50 patients in the AmB arm (3 possible IFI, 13 empirical antifungal therapy, and 1 withdrawal owing to difficult venous access) (P=0.66). Of the 29 patients who had a failure of prophylaxis unrelated to drug toxicity, computed tomography of the chest showed infiltrates in 10 patients with 3/12 in the voriconazole arm and 7/16 in the AmB arm (P=0.43). Drug-related serious adverse events were 6% versus 30% in voriconazole and AmB arms, respectively (P<0.01). Further, the total number of toxicities per patient in the AmB arm was significantly higher as compared with the voriconazole arm (P<0.0001) [14].

AFP with voriconazole can be useful in acute leukemia patients undergoing first remission-induction chemotherapy in settings in which there is a high risk of invasive *aspergillosis*. Chabrol *et al* assessed the impact of voriconazole or caspofungin prophylaxis in patients undergoing induction chemotherapy for acute leukemia in a hematology unit exposed to building work. Invasive *aspergillosis* was diagnosed in 21 patients (12%) in the non-prophylaxis group and four (4.5%) in the prophylaxis group (P=0.04). Pulmonary antecedents, neutropenia at diagnosis, and acute myeloid leukemia with high-risk cytogenetics were positively correlated with invasive *aspergillosis*, whereas primary prophylaxis was negatively correlated. Survival was similar in both groups. No case of *zygomycosis* was observed. The 3-month mortality rate was 28% in patients with invasive *aspergillosis* [15].

Prophylactic oral voriconazole 200 mg twice daily resulted in trends toward reduced incidences of lung infiltrates and hepatosplenic candidiasis and it is considered safe and well-tolerable. Vehreschild *et al* conducted a trial to analyze the efficacy and safety of voriconazole in the prevention of lung infiltrates during induction chemotherapy for AML. Incidence of lung infiltrates until day 21 was 0 in the voriconazole and 5 (33%) in the placebo group (P = 0.06). The average length of stay in the hospital was shorter in the voriconazole group (mean 31.9 days) than in the placebo group (mean 37.3 days, P = 0.09). Four patients were diagnosed with hepatosplenic candidiasis until a 4-week follow-up, all in the placebo group (P = 0.11) [16].

Initial therapy in patients with IA with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B Denning *et al* conducted a randomized trial to compare voriconazole with amphotericin B for primary therapy of invasive aspergillosis. A total of 144 patients in the voriconazole group and 133 patients in the amphotericin B group with definite or probable aspergillosis received at least one dose of treatment. At week 12, there were successful outcomes in 52.8% of the patients in the voriconazole group (complete responses in 20.8% and partial responses in 31.9%) and 31.6% of those in the amphotericin B group (complete responses in 16.5% and partial responses in 15.0%; absolute

Table I: Various studies evaluating the efficacy of antifungal prophylaxis

S. No.	Study	Number of patients	Prophylactic agent	Incidence of IFI	Mortality due to IFI	Dose
1.	Rotstein *et al* [15]	304	Fluconazole Placebo	13% 42%	6.7% 40%	400 mg daily
2.	Winston *et al* [16]	257	Fluconazole Placebo	10% 23%	11% 28%	400 mg daily
3.	Shah *et al* [17]	141	Fluconazole Voriconazole	6.6% 29%	9% 1.3%	6mg/kg/day (capped at 300 mg/day) 200 mg twice daily
4.	Mandhaniya *et al* [18]	100	Voriconazole Amphotericin B	4% 6%	2% 2%	6mg/kg/day for initial 2 doses followed by 4mg/kg/day twice daily 0.5mg/kg/day 0.5mg/kg/day thrice weekly
5.	Chabrol *et al* [19]	258	Voriconazole/ Caspofungin Placebo	4.5% 12.4%	NR	200 mg twice daily/ 70mg on day 1 followed by 50 mg daily IV
6.	Vehreschild *et al* [20]	25	Voriconazole Placebo	4% 33%	NR	200 mg twice daily
7.	Menichetti *et al* [22]	405	Itraconazole Placebo	0.5% 4%	0 2%	2.5mg/kg IV every 12 hours
8.	Rjinders *et al* [27]	271	Liposomal amphotericin B Placebo	4.3% 13.6%	0 16%	2.5 ml of 5 mg/ml solution inhalation 2 days per week
9.	Penack *et al* [28]	132	Liposomal amphotericin B Placebo	4.6% 20.2%	3.6% 4.5%	50 mg IV daily
10.	Wingard *et al* [29]	180	Micoconazole Placebo	1.1% 9%	0 4.4%	5 mg/kg IV every 8 hours
11.	Cornely *et al* [31]	602	Posaconazole Fluconazole/Itraconazole	2% 8%	2% 5%	200 mg oral suspension every 8 hours 400mg daily/ 200mg oral solution every 12 hours

NR: Not reported; IV: Intravenous;

difference, 21.2%; 95% confidence interval, 10.4 to 32.9). The survival rate at 12 weeks was 70.8% in the voriconazole group and 57.9% in the amphotericin B group (hazard ratio, 0.59; 95% confidence interval, 0.40 to 0.88). Voriconazole-treated patients had significantly fewer severe drug-related adverse events, but transient visual disturbances were common (occurring in 44.8% of patients) [17].

Itraconazole

Itraconazole has activity against Candida and *Aspergillus* species. Itraconazole, in the capsule formulation, may have erratic absorption, and no preventive effect could be observed when plasma levels were <250 ng/mL. Itraconazole oral solution showed a better bioavailability. Menichetti *et al* evaluated the efficacy and safety of itraconazole oral solution for preventing fungal infections in a randomized, multicenter trial with 405 patients. Patients received either 2.5 mg/kg itraconazole every 12 hours or no systemic antifungal prophylaxis. Proven and suspected deep fungal infection occurred in 24% of itraconazole recipients and 33% of placebo recipients (p 0.035). There was an absolute reduction of 3.5% in the incidence of candidemia with itraconazole (0.5% vs 4%; p 0.01). Deaths due to candidemia occurred in none of the itraconazole recipients compared with 2% in placebo recipients (p 0.06). The incidence of aspergillosis was 2% with itraconazole and the rates of mortality due to aspergillosis were similar in both arms. Side effects causing drug interruption occurred in 18% of itraconazole recipients and 13% of placebo recipients. They concluded that itraconazole oral solution was well-tolerated and effectively prevented proven and suspected deep fungal infection as well as systemic infection and death due to Candida species [18].

Two meta-analyses concluded that itraconazole was effective for preventing invasive fungal infections [19, 20] but one found that the protective effect from prophylaxis was limited to trials using itraconazole oral solution at a dose of 200 mg twice daily, a preparation that is poorly tolerated[20]. Formulation (oral solution greater than oral capsule), gastric acidity, and concomitant food intake affect the itraconazole's absorption.

In an open-label, comparative, multicenter study comparing voriconazole and itraconazole as primary prophylaxis in adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI, permanent discontinuation of voriconazole due to AEs was reported in 39.3% of subjects versus 39.6% of subjects in the itraconazole arm. Treatment-emergent hepatic AEs resulted in permanent discontinuation of study medication for 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole [21]. Robenshtok *et al* performed a systematic review and meta-analysis of randomized, controlled trials comparing systemic antifungals with placebo, no intervention, or other antifungal agents for prophylaxis in cancer patients receiving myelosuppressive chemotherapy (predominantly for acute leukemia) or undergoing HCT. In patients with acute leukemia, antifungal prophylaxis was associated with significant reductions in fungal-related mortality (RR 0.66, 95% CI 0.44-1.00) and documented invasive fungal infections (RR 0.69, 95% CI 0.53-0.90). However, AFP was associated with only a nonsignificant trend toward a reduction in all-cause mortality (RR 0.88, 95% CI 0.74-1.06). Prophylaxis with itraconazole suspension reduced documented IFI when compared with fluconazole, with no difference in survival, and at the cost of more adverse events [22].

Amphotericin B

Even though amphotericin B formulations have activity against *Aspergillus* and the agents of mucormycosis as well as Candida, they are generally not used for antifungal prophylaxis due to their adverse effects and insufficient evidence regarding their efficacy. The efficacy of amphotericin B as prophylaxis is not well established. The administration is by the parenteral route and has been associated with infusional toxicities and nephrotoxicity. Rjinders *et al* evaluated the efficacy of aerosolized liposomal amphotericin B in preventing invasive pulmonary *aspergillosis* in a randomized placebo-controlled trial of 271 patients (during 407 neutropenic episodes) who were expected to be neutropenic for at least 10 days. Aerosolized amphotericin B was associated with a significant reduction in the rate of IA (4.3% vs. 13.6%). No survival benefit was observed and there was a significantly greater incidence of adverse events, primarily cough, preventing adherence to the drug administration [23]. Aerosolized amphotericin B has not been directly compared with systemic antifungal prophylaxis. Amphotericin B or nystatin given as an oral suspension or lozenge had some benefit in reducing superficial infections (mostly Candida) in some studies, but, did not have a benefit in reducing colonization and systemic or invasive infections. This is not surprising since the usual portals of entry for *Aspergillus* and other molds are the sinuses and respiratory tract.

Penack *et al* performed a prospective, randomized, open-label trial to evaluate the efficacy of low-dose liposomal amphotericin B (L-AmB) to reduce the incidence of invasive fungal infections (IFI) in 132 patients with hematological malignancies and prolonged neutropenia (>10 days) following intensive chemotherapy. Patients received either 50 mg L-AmB every other day or no systemic antifungal prophylaxis. They reported a reduced incidence of proven or probable IFI with L-AmB (6.7% vs 35%; p 0.001). Invasive aspergillosis occurred less frequently in patients receiving L-AmB-prophylaxis (p 0.0057), whereas the reduction of invasive candidiasis did not reach statistical significance (p 0.0655). The incidence of IFI was 4.6% with L-AmB and 20.2% without prophylaxis (p<0.01). The reported adverse events, possibly related to L-AmB, were observed in 4.6% and L-AmB was discontinued in 2.8%. There were no grade 3 or 4 toxicities. They concluded that antifungal prophylaxis with low-dose L-AmB proved to be feasible and effective [24].

Miconazole

Prophylaxis with parenteral drugs like intravenous miconazole has been used only on a limited basis because of concerns about toxicity and overall effectiveness Wingard *et al* conducted a prospective, randomized trial in 180 patients to evaluate the efficacy of Miconazole. Patients received intravenous miconazole or placebo. Miconazole 5mg/kg was given every eight hours. Fungal sepsis occurred in only one patient receiving miconazole compared with eight patients receiving placebo (p = 0.03). Fatal fungal sepsis occurred in four patients receiving placebo and in none of the patients receiving miconazole (p = 0.08). There was no evidence for the development of resistance to polyenes or imidazoles in fungal isolates recovered from patients in this randomized trial or an

increase in Aspergillus infections in patients who received miconazole. They concluded that intravenous miconazole was more effective than placebo in preventing fungal sepsis in patients with chemotherapy-induced prolonged neutropenia [25].

Posaconazole

Oral posaconazole is available in two formulations, oral suspension, and delayed-release tablets. The absorption of the oral suspension is greatly improved by concomitant food, especially high-fat food[26]. Delayed-release tablets have the advantage of more reliable oral absorption and achieving higher blood levels as compared with oral suspension. Patients who are unable to take medications orally or who are expected not to absorb oral medications should be given IV posaconazole. Delayed-release tablets should be given as a loading dose of 300 mg (three 100 mg tablets) every 12 hours on the first day, followed by a maintenance dose of 300 mg (three 100 mg tablets) daily starting on the second day. The IV formulation should be given as a loading dose of 300 mg every 12 hours on the first day, followed by a maintenance dose of 300 mg daily starting on the second day. The dosing of the oral suspension is 200 mg three times daily. Due to differences in dosing, these formulations should not be used interchangeably.

Posaconazole prophylaxis reduced all-cause mortality (RR, 0.74; 95% CI, 0.56 to 0.98), fungal-related mortality, and IFI when compared with fluconazole. No difference was seen when fluconazole was compared with amphotericin B, in all-cause mortality, fungal-related mortality, any (documented, probable, and possible) IFIs, documented Candida or *Aspergillus* infections, and superficial fungal infections. Fluconazole resulted in a significant reduction of documented IFIs (RR, 0.49; 95% CI, 0.28 to 0.86) and more adverse events in the amphotericin group, necessitating discontinuation of the drug (RR, 6.67; 95% CI, 2.6 to 16.7). The use of posaconazole compared with fluconazole or itraconazole resulted in a reduction in all-cause mortality of borderline statistical significance (RR, 0.77; 95% CI, 0.59 to 1.01). Posaconazole prophylaxis yielded a significant reduction in documented invasive *Aspergillus* infections (RR, 0.22; 95% CI, 0.11 to 0.42). There was no difference in the prevalence of adverse reactions causing discontinuation of the study drug (RR, 0.88; 95% CI, 0.66 to 1.17). When fluconazole was compared with other antifungals with antimold activity, a trend for higher all-cause mortality was seen with fluconazole (12 trials; RR, 1.14; 95% CI, 0.95 to 1.37) and a significantly higher rate of fungal-related mortality, any IFI, and IFIs caused by Aspergillus species [22].

Cornely *et al* compared posaconazole with fluconazole or itraconazole in a multicenter randomized trial of 602 patients who were 13 years of age or older with prolonged neutropenia due to chemotherapy for AML or advanced MDS. Prophylaxis was given with each cycle of chemotherapy until recovery from neutropenia and complete remission, the occurrence of an IFI, or for up to 12 weeks, whichever came first. Posaconazole prophylaxis was associated with a significant reduction in proven or probable IFIs (2% vs. 8%, $p<0.001$). Significantly fewer patients in the posaconazole group had IA (1% vs. 7%, $p<0.001$) and associated with a significant reduction in all-cause mortality (16% vs. 22%). Survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole ($p = 0.04$). However, serious adverse events attributable to the drug were significantly more common with posaconazole (6% vs. 2%), although the rate of toxicity of all causes was similar between the two groups [27].

Isavuconazole

Isavuconazole is effective in the treatment of both *aspergillosis* and mucormycosis[28]. In a small phase II trial in patients with acute myelogenous leukemia undergoing induction therapy, Isavuconazole prophylaxis was well tolerated and reliably achieved trough serum concentrations of >1 micrograms/mL[29]. Although it has been approved for the treatment of IA and mucormycosis, there was an increased rate of breakthrough IFI, when used for primary prophylaxis compared with either voriconazole or posaconazole[30]. Rausch *et al* assessed 100 patients and reported nine IFIs in patients receiving isavuconazole prophylaxis compared with three patients receiving posaconazole and one patient receiving voriconazole. Most infections were due to molds (eg. *Aspergillus*, *Fusarium*, *Rhizopus* spp) and occurred primarily in neutropenic patients undergoing chemotherapy for AML [31]. An alternative for patients who cannot receive voriconazole or posaconazole is isavuconazole, although it has not been studied for prophylaxis in randomized controlled trials.

Echinocandins

The echinocandins (caspofungin, micafungin, anidulafungin) have a broader spectrum of activity, with the most common Candida species being susceptible, with an excellent safety profile. The disadvantages are its availability only as an IV formulation and its high cost. Micafungin is a well-tolerated and effective prophylactic antifungal agent. Park *et al* assessed 33 patients with AML receiving IV micafungin 50 mg prophylaxis. The median duration of micafungin treatment was 24 days (range 1-68), with proven IFI in one patient (1.5%) and possible fungal infection in two patients (3.1%). Three patients died during induction therapy, and invasive aspergillosis pneumonia was the cause of death for one of those patients. They concluded that the outcomes in patients with AML were similar to those of prophylactic posaconazole, indicating the usefulness of micafungin as a prophylactic antifungal agent during induction therapy[32]. Caspofungin has been approved by the FDA for the treatment of IA in patients who cannot tolerate or who are refractory to standard therapy. The echinocandins should not be utilized for initial monotherapy of IA. Caspofungin prophylaxis compared with fluconazole resulted in a significantly lower incidence of IFI and may be considered for prophylaxis in AML patients, although study interpretation is limited by early termination due to an unplanned interim analysis that appeared to have suggested futility[33].Current antifungal agents available for the therapy of systemic mycosis are shown in table II.

Duration

Based on the patient's clinical status and history of prior fungal infections, the duration of prophylaxis should be individualized. Primary prophylaxis against molds and/or Candida is typically continued until myeloid reconstitution has occurred in patients with acute leukemia. Prophylaxis is usually continued at least until myeloid reconstitution has occurred in patients who have a history of a prior IFI and who are receiving secondary prophylaxis during a period of myelosuppression. In such patients, follow-up imaging (CT scan of the organ involved in prior infection) and fungal markers (eg, Aspergillus galactomannan antigen, beta-D-glucan) are often obtained two to four weeks after AFP has been discontinued to ensure that reactivation has not occurred. Secondary prophylaxis is continued until completion of the course of chemotherapy in patients undergoing repeated courses of myelosuppressive chemotherapy.

Table II Current antifungal agents available for the therapy of systemic mycosis [38]

Antifungal spectrum	AMB	5FC	FLU	ITR	VOR	POS	ISA	CAS	MIC	ANI
Candida albicans	++	++	++	++	++	++	++	++	++	++
Candida glabrata	++	++	-	+	++	++	++	+	+	+
Candida parapsilosis	++	++	++	++	++	++	++	++	++	++
Candida tropicalis	++	++	++	++	++	++	++	++	++	++
Candida krusei	++	+	-	+	++	++	++	++	++	++
Candida lusitaniae	-	++	++	++	++	++	++	++	++	++
Aspergillus fumigatus	++	-	-	+	++	++	++	+	+	+
Cryptococcus neoformans	++	++	++	++	++	++	++	-	-	-
Mucorales	++	-	-	-	-	++	++	-	-	-
Fusarium spp.	+	-	-	+	++	++	++	-	-	-
Scedosporium spp.	+	-	-	+	+	+	+	-	-	-
Blastomyces dermatitidis	++	-	+	++	++	++	++	-	-	-
Coccidioides immitis	++	-	++	++	++	++	++	-	-	-
Histoplasma capsulatum	++	-	+	++	++	++	++	-	-	-

5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MIC, micafungin; POS, posaconazole; VOR, voriconazole;+, active; ++, very active; -, not active;

Empiric Antifungal Therapy

An empiric antifungal agent should be added after four to seven days in high-risk neutropenic patients who are expected to have a total duration of neutropenia >7 days who have persistent or recurrent fever and in whom reassessment does not yield a cause. In patients who have not been receiving AFP, Candida species are the most likely cause of IFI. The 2016 Infectious Diseases Society of America guidelines state that empiric antifungal therapy should be considered in critically ill patients who are at risk for invasive candidiasis and who have persistent fevers and no other known cause of fever; the decision regarding empiric therapy should be based upon clinical assessment of risk factors, surrogate markers for invasive candidiasis (eg, beta-D-glucan), and/or culture data from non-sterile sites [34].

Pre-Emptive Antifungal Therapy

Pre-emptive approach involves targeted screening of high-risk patients for markers of colonization and/or infection in an attempt to prevent invasive infection which involves checking fungal markers, such as the *Aspergillus galactomannan* antigen, *Aspergillus* polymerase chain reaction (if available), and beta-D-glucan, and chest CT scanning. A rising or positive serum galactomannan test, or the finding of suspicious abnormalities on CT scans, are triggers to start full-dose anti-mold drug therapy in febrile high-risk patients while simultaneously pursuing a definitive diagnosis [35]. This approach is best suited for patients receiving prophylaxis with an anti-yeast agent, such as fluconazole, where the concern is mainly mold pathogens and one is considering broadening the coverage to include an anti-mold agent. Advantages include reducing the perceived unnecessary use of empirical antifungal therapy with its attendant toxicity and cost [36].

SUMMARY OF PRIMARY PROPHYLAXIS

- For patients with AML undergoing induction therapy who are expected to develop severe oral and/or gastrointestinal mucositis, primary prophylaxis is recommended [39].
- Fluconazole prophylaxis at a dose of 400 mg per day has been shown to effectively decrease fungal colonization, invasive infection, and fungal infection-related mortality in patients with AML [11].
- A mold-active triazole is recommended where the risk of invasive aspergillosis is >6%, such as in patients with AML during the neutropenic period associated with chemotherapy [39].
- Therefore, for selected patients who are expected to experience prolonged severe neutropenia (ANC<500 cells/microL for >7 days) due to intensive chemotherapy for AML, prophylaxis against invasive mold infections and Candida species with posaconazole or voriconazole is recommended rather than targeted anti-Candida prophylaxis with fluconazole.
- Prophylactic dose of voriconazole is 200 mg orally twice daily and 4 mg/kg/dose (rounded to nearest 50 mg) twice a day in pediatric patients (maximum 200 mg twice a day) [13].
- Posaconazole delayed-release tablets should be given as a loading dose of 300 mg (three 100 mg tablets) every 12 hours on the first day, followed by a maintenance dose of 300 mg (three 100 mg tablets) daily starting on the second day. The IV formulation of posaconazole should be given as a loading dose of 300 mg every 12 hours on the first day, followed by a maintenance dose of 300 mg daily starting on the second day. The dosing of the oral suspension of posaconazole is 200 mg three times daily. The delayed-release tablets, the IV formulation, and the oral suspension should not be used interchangeably due to differences in dosing.

Secondary Prophylaxis

Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection. A high risk for recurrence of infection with further anti-leukemic therapy is seen in patients who have a history of a prior IFI, especially Aspergillus infections. Continued treatment after initial control (so-called secondary prophylaxis) can prevent the reactivation of infection in most patients and permit further anti-leukemic therapy. Antifungal prophylaxis with a mold-active agent is recommended for patients with a history of prior IA receiving myelosuppressive chemotherapy with an anticipated prolonged neutropenic period of at least two weeks[40]. Voriconazole is the first-line agent for Aspergillus and has been best studied as secondary prophylaxis. Secondary prophylaxis should be selected based on the Candida species for patients with prior Candida infections.

SCOPE FOR FURTHER RESEARCH

There are certain key knowledge gaps related to AFP among children and adolescents with AML.

- Identification of personalized risk factors for IFI, which allows for more targeted prophylaxis among patients with higher risk.
- Determining the efficacy of prophylaxis with mold-active agents as compared to fluconazole prophylaxis combined with sensitive diagnostic tests and procedures to detect IFI.
- Determining the risks and benefits of prophylaxis with lipid formulations of amphotericin as compared to other mold-active agents.
- In the era of immunotherapy, determining the risk for IFI.
- Evaluating the role of therapeutic drug monitoring in guiding the prophylactic doses of mold-active azoles.
- Describing the best ways for the development and implementation of a fungal surveillance program and evaluating antifungal resistance after implementation.
- Assessing the role of environmental interventions such as high-efficiency particulate air filtration in the prevention of IFI.

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