Use of antifungal drugs in hematology

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Invasive fungal disease represents a major complication in hematological patients. Antifungal agents are frequently used in hematologic patients for different purposes. In neutropenic patients, antifungal agents may be used as prophylaxis, as empiric or preemptive therapy, or to treat an invasive fungal disease that has been diagnosed. The hematologist must be familiar with the epidemiology, diagnostic tools and strategies of antifungal use, as well as the pharmacologic proprieties of the different antifungal agents. In this paper the principal antifungal agents used in hematologic patients will be discussed as will the clinical scenarios where these agents have been used.

Keywords: *Antifungal agents; Mycoses; Aspergillosis*

Introduction

Invasive fungal disease (IFD) represents a major complication in hematological patients. These infections are particularly frequent in patients with hematological malignancies who develop prolonged and severe neutropenia, such as patients with acute myeloid leukemia (AML) and in hematopoietic stem cell transplant (HSCT) recipients[1]. The problem is aggravated by the fact that most IFD are difficult to diagnose and because host factors are key determinants of the outcome, resulting in a prognosis that is usually poor, especially if immunodeficiency persists.

Antifungal agents are frequently used in hematologic patients for different purposes. In neutropenic patients, antifungal agents may be used as prophylaxis (for at-risk patients), as empiric therapy, or to treat an IFD that has been diagnosed. Empiric therapy refers to the start of an antifungal agent provided to neutropenic patients with unexplained, persistent or recurrent fever despite appropriate antibiotic therapy[2]. In addition to prophylaxis, empiric and pathogen-directed antifungal therapy, a fourth modality of antifungal use has been recently advanced, called preemptive or diagnostic-driven antifungal therapy[3].

Antifungal drugs in hematology

The antifungal drugs frequently used in hematologic patients belong to the following classes: the polyenes, the azoles, and the echinocandins. Tables 1 and 2 summarize the pharmacologic characteristics and the spectrum of the antifungal agents. Among the polyenes, deoxycholate amphotericin B (d-AMB) has been largely used in hematologic patients despite severe and frequent side effects. However, with the availability of the lipid formulations and other drug classes, its use does not seem justifiable in the hematology setting anymore, given the complexity of these patients, who receive many concomitant nephrotoxic drugs such as antineoplastic agents, immunosuppressants and anti-infective drugs. Attempts to decrease d-AMB toxicity by adding lipid emulsions[4] or by administrating the drug by continuous infusion[5] are not recommended because although its use may be associated with less acute adverse events, the efficacy has not been proved.

There are three commercially available lipid formulations of amphotericin B: liposomal amphotericin B (L-AMB), amphotericin B lipid complex (ABLC) and amphotericin B in colloidal dispersion (ABCD). Data on head to head comparisons between the different lipid formulations are generally not available, with the exception of a study of empiric therapy in neutropenic patients that compared L-AMB with ABLC[6]. In this study, L-AMB was associated with fewer side effects, including renal toxicity. In general, the three lipid formulations are less nephrotoxic than d-AMB, with the frequency of acute infusion-related adverse events being the highest with ABLD, followed by d-AMB and ABLC, and L-AMB. Standard daily doses of the lipid formulations are 3 mg/kg for L-AMB and 5 mg/kg for ABLC and ABCD. Higher daily doses of L-AMB (10 mg/kg) did not show superiority over the 3 mg/kg dose used in the treatment of IFD and was associated with more side effects[7]. Notwithstanding

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Table 1 - Systemic antifungal agents used in hematologic patients

Drug	Route	Toxicity	Drug interactions*
Drug class: Polyene			
d-AMB	IV	Acute, infusion-related: fever, chills, hypotension, tachycardia Long-term: hypokalemia, hypomagnesemia, anemia, renal dysfunction	Additive deleterious effect on renal function if given with other nephrotoxic drugs such as aminoglycosides, cyclosporine etc.
L-AMB	IV	Fewer acute and long-term side effects	Same as d-AMB, but less problematic
ABLC	IV	Fewer long-term side effects but similar rates of acute toxicity compared to d-AMB	Same as d-AMB, but less problematic
ABCD	IV	Fewer long-term side effects but higher rates of acute toxicity compared to d-AMB	Same as d-AMB, but less problematic
Drug class: Azole			
Fluconazole	PO, IV	Skin rash, nausea, abdominal pain, headache (all occasional)	↓ metabolism of: busulfan, benzodiazepines, carbamazepine, corticosteroids, cyclosporine, tacrolimus ↑ serum concentration of: imatinib May ↑ QTc prolongation of: ciprofloxacin, nilotinib
Itraconazole	PO**	Similar to fluconazole, but more frequent (with oral solution)	Similar to fluconazole plus: Antacids, H2 antagonists and proton pump inhibitors ↓ serum concentration of itraconazole ↑ serum concentration of: bortezomib, vinblastine, vincristine (↑ toxic effects!!) ↓ serum concentration of: brentuximab
Voriconazole	PO, IV	Auditory and visual hallucinations, visual changes, rash, nausea, liver dysfunction	↑ toxic effects: vincristine and vinblastine ↑ serum concentration: bortezomib, brentuximab, corticosteroids, imatinib, tacrolimus ↓ metabolism: busulfan, cyclosporine ↑ QTc prolongation: ciprofloxacin, nilotinib
Posaconazole	PO	Headache, diarrhea, nausea, liver dysfunction	Similar to voriconazole H2 antagonists and proton pump inhibitors ↓ serum concentration of posaconazole
Drug class: Echinocandin			
Caspofungin	IV	Fever, diarrhea, hepatic dysfunction, hypokalemia	Caspofungin ↓ serum levels of tacrolimus by 20% Cyclosporine ↑ serum levels of caspofungin by 35%
Micafungin	IV	Gastrointestinal symptoms, infusion-related reactions	Micafungin ↓ clearance of cyclosporine by 16%
Anidulafungin	IV	Nausea, hypokalemia	Cyclosporine ↑ serum levels of anidulafungin by 22%

* Drug interactions relevant to the hematologic patient; ** Oral solution and IV preparation not available in Brazil
d-AMB = deoxycholate amphotericin B; IV = intravenous; L-AMB = liposomal amphotericin B; ABLC = amphotericin B lipid complex; ABCD = amphotericin B colloidal dispersion; PO = oral route; ↓ = decrease; ↑ = increase

Table 2 - Microbiologic spectrum of the different antifungal agents

	AMB	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Echinocandins
Candida albicans	+++	+++	+++	+++	+++	+++
Candida tropicalis	+++	+++	+++	+++	+++	+++
Candida parapsilosis	+++	+++	+++	+++	+++	+++
Candida glabrata	++	+/-	+/=	+	+	+++
Candida krusei	+++	-	+/-	+++	+++	+++
*Aspergillus fumigatus**	+++	-	+++	+++	+++	++**
Aspergillus flavus	+++	-	+++	+++	+++	++**
Aspergillus terreus	-	-	+++	+++	+++	++**
Fusarium species	+	-	-	-/+	-/+	-
Agents of mucormycosis	++	-	-	-	+	-

* Molecular studies show that *Aspergillus fumigates* comprises a complex of various species, some of which may be less susceptible to antifungal agents; ** ++ because the echinocandins have fungistatic effect against *Aspergillus* species

these shortcomings, higher doses are frequently given in real life, especially in the treatment of severe infections such as invasive fusariosis and mucormycosis, or if the patient is not responding to standard doses. Although common, these practices are not evidence-based. Regardless of the differences in side effects between the three lipid formulations of AMB, they are equally effective when compared with d-AMB, and this is another reason to abandon the use of d-AMB in hematologic patients.

Amphotericin B has the largest spectrum of all antifungal agents, and despite the fact that it has been used for a long time, resistance is rarely observed in the clinical practice. The preparations of AMB have been used in hematologic patients in the empiric antifungal therapy of febrile neutropenia[6-10], as well as in the treatment of various IFD, including candidemia, acute and chronic disseminated candidiasis, aspergillosis, fusariosis, mucormycosis and others[7,11-13].

The azoles are another class of antifungal agents. Fluconazole is available in both oral and intravenous preparations and is largely used in hematologic patients, mostly as prophylaxis against invasive candidiasis in allogeneic HSCT[14,15] and in patients with AML receiving induction chemotherapy regimens with high potential to induce severe gastrointestinal mucositis[16]. The usual prophylactic dose is 400 mg once per day for both the oral and intravenous preparations. In addition to prophylaxis, fluconazole can be used for the treatment of candidemia, although its use for this indication is limited by the fact that most hematologic patients have received fluconazole previously, and therefore are more likely to have infections caused by less-susceptible species (*Candida glabrata* and *Candida krusei*)[17]. Another indication of fluconazole is in the long-term treatment of chronic disseminated candidiasis[18]. The chronic use of fluconazole, especially intermittently and at low doses, is the ideal scenario for the development of resistance which is mediated by various mechanisms, including mutations in the drug target and efflux pumps[19]. Once resistance develops, cross resistance with other agents of the class is the rule. Therefore, patients with candidiasis caused by a fluconazole-resistant (or less-susceptible) isolate are best treated with a drug belonging to another class.

Itraconazole is available in capsules, oral preparation and intravenous formulation. It has a broader spectrum than fluconazole, including activity against *Aspergillus*. While both the intravenous preparation and oral solution have been used in hematologic patients as prophylaxis for IFD in allogeneic HSCT[20,21], itraconazole capsules are not effective as prophylaxis in hematologic patients because of its poor oral absorption[22]. Neither the oral nor the intravenous preparation of itraconazole is available in Brazil, thus strongly limiting the use of this agent in hematologic patients.

The newer generation of azoles is represented by voriconazole and posaconazole. Voriconazole is available in oral and intravenous preparations, and has its main indication in hematology as primary treatment for invasive aspergillosis[23]. Other scenarios in which voriconazole is frequently used include primary prophylaxis of high risk patients (allogeneic HSCT or even AML patients in induction remission), secondary prophylaxis in patients with prior history of invasive aspergillosis, empiric or preemptive antifungal therapy, and treatment of fusariosis[9,24-26].

Hematologic patients receiving voriconazole usually have variations in serum levels due to both variable absorption of the oral preparation and metabolism. In hematologic patients the bioavailability of the oral preparation is about 63%, contrasting with the excellent bioavailability (80-95%) in healthy subjects[27]. In addition, polymorphisms in the CYP2C19 P450 enzyme drive serum levels of voriconazole. The frequency of these polymorphisms varies according to the ethnic group, with Asian patients being more frequently homozygous poor metabolizers (and thus having higher serum levels of voriconazole)[28]. The usual intravenous (300 mg twice daily) and oral (200 mg twice daily) doses of voriconazole have been challenged recently, and a study suggested that higher oral doses (300 or 400 mg twice daily) are needed to achieve optimal serum levels[27]. The ideal scenario would be to monitor serum levels in non-responding patients or in those with neurologic or hepatic toxicity, but this is not practical in the overwhelming majority of centers worldwide. Although the occurrence of resistance is less frequent than with fluconazole, *Candida* isolates may be resistant to voriconazole. In addition, recent reports of a few azole-resistant *Aspergillus* species have been reported, mostly in Europe[29]. The clinical relevance of these findings is not known at the present time.

Posaconazole is available as an oral solution. Its main indication is prophylaxis in patients with AML or myelodysplasia (MDS) receiving induction remission therapy[30] and in allogeneic HSCT recipients with severe graft versus host disease (GVHD) or receiving intensive systemic immunosuppressive therapies[31]. Therapeutic drug monitoring is usually recommended for posaconazole although the adequate trough serum level has not been established. The oral bioavailability of the oral solution is variable and dependent on a fatty meal. The usual dose for prophylaxis is 200 mg three times a day. An oral tablet and an intravenous formulation of posaconazole are under development.

Isavuconazole is an azole antifungal agent with the largest antifungal spectrum of all azoles; it is available in oral and intravenous preparations. Phase III studies with this drug are under way.

The other class of antifungal agents used in hematologic patients is the echinocandins. Different from the other classes that have their target in the fungal membrane, the echinocandins act on the fungal cell wall. This predicts a very good safety profile for these drugs since human cells do not have a cell wall. The three agents are caspofungin, micafungin and anidulafungin. There are some differences between the three agents, but in general they can be used interchangeably. Caspofungin and anidulafungin need a loading dose on the first day of therapy (70 mg and 200 mg, respectively), whereas micafungin does not. The adult daily dose is 50 mg for caspofungin and 100 mg for anidulafungin and micafungin. Caspofungin is the agent most studied in neutropenic patients. Although experience with anidulafungin in neutropenic patients is very limited[32], a neutropenic murine invasive candidiasis model showed similar activities for anidulafungin and caspofungin[33]. The main indication of the echinocandins is primary treatment of candidemia and invasive candidiasis[13,34-37]. In addition, caspofungin has been extensively used as empiric antifungal therapy in persistently neutropenic patients[38,39]. Other potential uses of the echinocandins are as secondary prophylaxis[40,41] and in combination with voriconazole

in the treatment of invasive aspergillosis[42]. Resistance to echinocandins among *Candida* isolates has been increasingly reported and involves mutations in the drug target[43].

Strategies of antifungal use in hematology

Antifungal agents can be used in different ways in patients with hematologic diseases: as prophylaxis, empiric therapy, preemptive therapy (or diagnostic-driven), and for the treatment of a documented IFD.

Antifungal prophylaxis

Antifungal prophylaxis in hematologic patients is very tempting because the incidence of IFD is high, the diagnosis is not easily performed, and the mortality may be very high. Nevertheless, prophylaxis is not indicated in all patients. In general, the higher the incidence of an IFD and the shorter the period at risk, the more likely prophylaxis will work. The problem is that both an estimation of the magnitude (probable incidence) and the duration of risk are not easily advanced at the bedside.

The first question to be answered in order to define if antifungal prophylaxis is indicated is if the patient is at risk for both invasive candidiasis and invasive mould disease (mostly invasive aspergillosis). The main risk factors for invasive candidiasis are neutropenia, gastrointestinal mucositis and a central venous catheter. By contrast, prolonged (usually > 10 days) and severe (< 100/mm³) neutropenia and severe T-cell immunodeficiency are the main risk factor for invasive aspergillosis. If the patient is at risk for invasive candidiasis only, fluconazole is the agent of choice for prophylaxis, given at a dose of 400 mg daily (adult dose). The strongest benefit of fluconazole prophylaxis is observed in allogeneic HSCT recipients. In these patients, two randomized clinical trials showed that fluconazole reduced the frequency of superficial and systemic candidiasis, as well as infection-related mortality[14,15]. In addition, in one of these trials fluconazole was given until day +75 post-transplant, and a post-hoc analysis of the trial showed that fluconazole was associated with prolonged protection against invasive candidiasis, even beyond the period of prophylaxis[44]. The benefit of prophylaxis against invasive candidiasis was not as apparent in other settings, such as in patients with acute leukemia and autologous HSCT recipients[45]. However, the ineffectiveness of fluconazole in non-HSCT neutropenic patients is probably related to the heterogeneity of the populations of neutropenic patients studied (with different incidences of invasive candidiasis) rather than an absence of efficacy. Fluconazole is not effective in preventing infection caused by *Candida krusei* and most *Candida glabrata* isolates, which exhibit high minimal inhibitory concentrations (MICs) to fluconazole.

Other agents that can be used as prophylaxis for invasive candidiasis include micafungin[46], itraconazole (oral solution and intravenous preparation only, not available in Brazil)[20,21], voriconazole[24,47] and posaconazole[31]. The latter two drugs are indicated if anti-mould prophylaxis is also needed.

The group with the highest incidence of invasive aspergillosis is represented by patients with AML or MDS undergoing induction remission chemotherapy, and allogeneic HSCT recipients. In these patients, the at-risk period encompasses both early pre-engraftment (in which neutropenia is the leading risk factor) and post-engraftment (T-cell immunodeficiency due to GVHD and its treatment).

In the setting of AML/MDS, posaconazole (200 mg 3x/day) was superior to fluconazole or itraconazole oral solution in a large randomized controlled trial, and is considered the drug of choice for anti-*Aspergillus* prophylaxis[30]. Voriconazole has not been tested in trials of AML patients, but has been frequently used as prophylaxis.

In allogeneic HSCT, itraconazole oral solution, given in the pre- and post-engraftment periods, was tested against fluconazole in two randomized clinical trials[20,21]. One trial showed a reduction in the incidence of IFD in itraconazole recipients[21], while the other showed a reduction in the incidence of invasive mould disease[21]. The problem with itraconazole oral solution (once again, not available in Brazil), is that as high as one fourth of patients discontinued the study drug due to gastrointestinal intolerance. Another option in the allogeneic HSCT setting is posaconazole. In a randomized trial, this agent was compared with fluconazole in patients with GVHD (however, in the post-engraftment period only)[31]. There was a significant difference in the incidence of invasive aspergillosis favoring the posaconazole arm (2.3% vs. 7%, p-value = 0.006), although for the primary endpoint (incidence of IFD on day 112 of prophylaxis) there was a non-significant advantage of posaconazole (p-value = 0.07).

Another option for anti-mould prophylaxis in allogeneic HSCT recipients is voriconazole. In one randomized study, voriconazole was compared with itraconazole oral solution, given just after conditioning regimen until > 100 days[47]. Among 465 patients randomized, only eight IFD were diagnosed, three in the voriconazole arm (1.3%) and five in the itraconazole arm (2.1%). As in the other trials of itraconazole, gastrointestinal intolerance was significantly more frequent in itraconazole recipients. In another trial, allogeneic HSCT recipients received either voriconazole or fluconazole given in both pre- and post-engraftment periods[24]. The number of cases of invasive aspergillosis was lower in the voriconazole arm, but the difference was not statistically significant (9 vs. 17 cases, p-value = 0.09). An interesting feature of this trial is that all patients were monitored with bi-weekly (until day 60) or weekly (from day 60 to day 100) serum galactomannan tests, with empiric antifungal therapy being initiated based on positive galactomannan tests and other findings (radiology or clinical parameters). Therefore, another way of interpreting these results is that fluconazole prophylaxis plus structured galactomannan monitoring (and initiation of appropriate antifungal therapy) is as good as voriconazole prophylaxis.

Outside the setting of AML/MDS and allogeneic HSCT no formal recommendations can be made regarding antifungal prophylaxis. In autologous HSCT recipients the use of antifungal agents is controversial. Recent guidelines recommend administering anti-*Candida* prophylaxis to a sub-population of autologous recipients who have underlying hematologic malignancies (for example, lymphoma, leukemia or myeloma) and who have or will have prolonged neutropenia and mucosal damage from intense conditioning regimens or graft manipulation, or have received fludarabine or 2-CDA within 6 months before HSCT, with a BIII level of evidence (moderate strength of

Table 3 - Antifungal agents used as empiric/preemptive therapy based on the prophylactic strategy

Prophylaxis	Etiology of breakthrough IFD	Antifungal agent for empiric / preemptive therapy	Comments
No	*Candida*>>>*Aspergillus*>>> Other moulds*	Fluconazole, caspofungin	Risk of aspergillosis depends on duration of neutropenia and T-cell immune status
Fluconazole	*Aspergillus* >>> Other moulds* ≥ *Candida*	Caspofungin, L-AMB**, voriconazole	In preemptive strategy, voriconazole (or L-AMB) is preferred if clinical parameters suggest a diagnosis of invasive aspergillosis
Posaconazole or voriconazole	Other moulds* ≥ *Aspergillus* ≥ *Candida*	L-AMB**	Breakthrough infection may be due to non-susceptible agent or low serum levels of the azole

IFD = invasive fungal disease; L-AMB = liposomal amphotericin B
* Other moulds: Fusarium, agents of mucormycosis;
** Other lipid formulations of amphotericin B may be used, but L-AMB has been more extensively studied

recommendation based on the opinion of experts)[48]. In addition, although some autologous HSCT recipients are at high risk for developing invasive aspergillosis (especially patients with multiple myeloma having received intensive chemotherapeutic regimens before transplant)[49], no formal recommendations can be made regarding anti-mould prophylaxis in this setting.

The same is true for other hematologic patients. Patients with multiple myeloma (receiving or not autologous HSCT) and patients with chronic lymphocytic leukemia (CLL) represent two emerging underlying conditions in invasive aspergillosis. Both groups have as background severe T-cell immunodeficiency plus some neutropenia (that may not necessarily be severe and prolonged), caused by intensive treatment over the course of years (myeloma)[50] or the use of T-cell immunosuppressants such as fludarabine and (especially) alemtuzumab (CLL)[51]. Despite the higher risk for invasive aspergillosis, anti-mould prophylaxis is usually not given in these two scenarios.

Empiric and diagnostic driven antifungal therapy

The initiation of an antifungal agent in neutropenic patients with unexplained persistent or recurrent fever despite appropriate antibiotic therapy is considered standard of care although this strategy has never been validated by solid evidence. The two studies that launched the basis for empiric antifungal therapy (both published in the 1980s) showed non-significant differences in outcomes favoring empiric therapy, with strong limitations in both studies, related to the small sample size[52,53]. Nevertheless, the strategy became standard of care because the incidence of IFD was increasing and there were no diagnostic tools. The scenario has changed: the epidemiology, at-risk groups and natural history of IFD are well characterized, and various diagnostic tools have been incorporated into clinical practice, including high resolution computed tomography (CT) scan and serum galactomannan testing. On the other hand, the empiric therapy strategy uses fever as the trigger for starting an antifungal agent. The problem is that fever is non-specific and this results in a large group of patients that end up receiving an antifungal agent without need. A preemptive strategy has been developed to replace empiric therapy that is based on the search for other parameters that might be more precise in defining who will need to receive an antifungal agent. These parameters are clinical signs, images and

biomarkers, such as polymerase chain reaction (PCR - still under development) and the galactomannan test. Because the initiation of an antifungal agent is driven by diagnostic tests, some authors prefer to call diagnostic driven antifungal therapy[3].

The empiric and the preemptive strategies were tested in one randomized clinical trial in patients receiving chemotherapy or autologous HSCT[54]. The preemptive therapy was started if patients presented at least one of the following: pneumonia, sinusitis, mucositis (Grade 3 or higher), septic shock, skin lesions suggestive of IFD, unexplained neurologic symptoms, severe diarrhea, periorbital inflammation, splenic or hepatic abscess, *Aspergillus* colonization or positive serum galactomannan. The antifungal drug was d-AMB or L-AMB (depending on the renal function). Although probable or proven IFD was more frequent in the preemptive arm, there were no differences in survival. The preemptive strategy has also been tested in non-randomized studies using PCR[55], chest and sinus CT scan[56], or a combination of parameters including serum galactomannan[57]. The preemptive strategy requires an integrated action involving different professionals and capabilities (availability of CT scan, serum galactomannan in real time, and others).

Regardless of the strategy – empiric or preemptive – the choice of the antifungal drug depends on what prophylactic strategy has been applied. Table 3 shows different options of empiric/preemptive therapy based on the prophylactic strategy and the expected etiology for IFD.

Treatment of documented invasive fungal disease

Candidemia

In Brazil, *C. albicans*, *C. parapsilosis* and *C. tropicalis* account for > 80% of cases of candidemia[58]. However, if the patient is receiving fluconazole prophylaxis, infection due to *C. glabrata* and *C. krusei* are more likely to occur[17].

There is little data on the treatment of candidemia in neutropenic patients. Among 10 randomized trials of different antifungal agents for the treatment of candidemia/ invasive candidiasis[13,34-37,59-63], only five included neutropenic patients[13,35-37,63], and the proportion of such patients was usually < 10%. Taking these limitations into consideration, an echinocandin is considered the drug of choice as primary

treatment for candidemia (caspofungin 70 mg on day 1 and 50 mg thereafter; micafungin 100 mg daily or anidulafungin 200 mg on day 1 and 100 mg thereafter). Step-down therapy to fluconazole (400 mg once a day) after a few days of intravenous echinocandin is a good alternative, provided that the patient is improving and the isolate is not *C. glabrata* or *C. krusei*. An alternative to an echinocandin is L-AMB (3 mg/kg daily). Catheter management should be individualized, considering that in the majority of cases of candidemia, the gut is the origin of infection[64]. A reasonable approach is to start therapy with an echinocandin or L-AMB and re-evaluate after 3-4 days of therapy[65], unless clinical signs of tunnel infection are clearly evident. In these circumstances, prompt removal of the catheter is advised. For the treatment of chronic disseminated candidiasis, L-AMB followed by oral fluconazole or voriconazole for prolonged periods is the treatment of choice. The use of corticosteroids may accelerate clinical improvement[66,67].

Aspergillosis

The drug of choice for primary treatment of invasive aspergillosis is voriconazole[23]. Treatment usually is started with the intravenous preparation (6 mg/kg twice a day on day 1 and 4 mg/kg thereafter), although a study suggested that starting therapy with oral voriconazole is not associated with poorer outcomes[68]. A recent study suggested that higher doses of oral voriconazole (300 to 400 mg twice a day) are needed in order to achieve therapeutic serum levels of the drug[27].

An alternative to voriconazole is L-AMB. Although a head to head comparison between L-AMB and voriconazole has not been performed, response rates and survival of patients treated with two doses of L-AMB (3 vs. 10 mg/kg daily)[7] were comparable to those obtained in the voriconazole trial[23].

A recent randomized study compared voriconazole with the combination of voriconazole and anidulafungin in the treatment of invasive aspergillosis[42]. The 6-week survival was 80.7% in patients receiving combination therapy and 72.5% in patients receiving voriconazole (p-value = 0.08). A sub-group analysis of patients with baseline positive serum galactomannan showed a statistically significant survival advantage of the combination arm.

Fusariosis

The outcome of invasive fusariosis is very poor, with a 21% 90-day probability of survival in patients with hematologic diseases[11] and only 13% in HSCT recipients[69]. The drug of choice is a lipid formulation of AMB. We recently analyzed the outcome of 158 cases of fusariosis, and observed that the outcome has improved in the last decade. Multivariate analysis showed that receipt of d-AMB was associated with poor outcome. By contrast, survival was improved with the use of voriconazole (data in preparation for publication).

Mucormycosis

The recommended treatment of mucormycosis is a lipid preparation of AMB. Although strong data regarding the dose are

lacking, some experts recommend higher doses[12]. Posaconazole is also active against some agents of mucormycosis, and may be used as step-down therapy once patient is responding to intravenous AMB.

Conclusion

Hematologic patients are at risk of IFD, and therefore antifungal agents are an important part of the therapeutic armamentarium of any hematology unit. The hematologist must be familiar with the epidemiology, diagnostic tools and strategies of antifungal use. In addition, basic knowledge about the pharmacologic proprieties of the different antifungal agents is critical in order to best use these agents. This includes the antifungal spectrum of the agents, doses, side effects and drug interactions that may compromise the management of infection and the underlying hematologic disease.

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