

Azole antifungal in Hematology: Interactions & Opportunities in the era of new treatment in hematological malignancy and immunosuppressed with antifungal

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Outline

Q1. Which is associated with potential risk for IFD

Q2. New evidence to support and guide the use of established prophylactic agents

Q3. New options for antifungal prophylaxis

Q4. What critical drug-drug interactions should clinician be aware of and what is the need for TDM in the era of targeted and immune-based therapies

Q5. How could antifungal prophylaxis recommendations be implemented into practice

Case sharing

Introduction

Treatment in hematological malignancies has undergone a paradigm shift

- Targeted therapy
 - Immune checkpoint inhibitors
 - CART
 - Stem cell transplantation
- > improve in OS, but associated with potential risk of IFD.

Q1. Which is associated with potential risk for IFD

Antifungal prophylaxis guidelines 2021

Table 1 Established risk groups for IFD and recommended antifungal prophylaxis coverage in adults

Risk level	Risk groups	Recommended prophylaxis†	SoR	QoE
High risk >10% incidence of IFD	Neutrophil $<0.1 \times 10^9/L$ for >3 weeks or $<0.5 \times 10^9/L$ for >5 weeks (e.g. allogeneic HSCT) Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils $<1 \times 10^9/L$ for >1 week Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks Unrelated, mismatched or cord blood allogeneic HSCT GVHD – extensive or severe AML – induction/reinduction ALL – induction/reinduction MDS	First line: Posaconazole Alternate agents: Voriconazole Itraconazole Micafungin Liposomal amphotericin Isavuconazole	A	I
Low risk Less than 5% incidence of IFD	Autologous HSCT (e.g. patients at high risk for mucositis) Allogeneic HSCT with expected neutropenia <14 days Lymphoma (e.g. intensive/dose-escalated therapy)	First line: Fluconazole Alternate agents: Echinocandins Itraconazole	B	II (context dependent; level I evidence in setting of alloHSCT)
Very low risk‡ Less than 5% incidence of IFD No mucositis	Other lymphoproliferative neoplasms (e.g. standard chemotherapy for lymphoma, induction therapy for myeloma, treatment-naïve CLL) Other myeloproliferative neoplasms Treatment for solid organ tumours	No prophylaxis	B	II

†Please refer to Table 4 for summary of recommendations and level of evidence supporting choice of antifungal prophylaxis agents.

‡Consider that low and/or sporadic occurrence is not equal to no risk and is dependent on underlying treatment regimen, previous and cumulative treatments.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; GVHD, graft versus host disease; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease; MDS, myelodysplastic syndrome; QoE, quality of evidence; SoR, strength of recommendation.

Q1. Which is associated with potential risk for IFD

Antifungal prophylaxis guidelines 2021

Table 2 Summary of IFD rates associated with emerging use of new generation cancer therapies

Therapy	Population	IFD rates (%)	Comments
BTK inhibitor (e.g. ibrutinib)	Relapsed/refractory B-cell lymphoproliferative disorder	3–12	Rates of 1% reported in clinical trials of BTK inhibitors Invasive aspergillosis with CNS involvement up to 40% <i>Cryptococcus</i> spp. <i>Pneumocystis jirovecii</i> pneumonia
	Primary CNS lymphoma	5–44	In combination with corticosteroids and conventional chemotherapy <i>Pneumocystis jirovecii</i> pneumonia
PI3K inhibitor (e.g. idelalisib)	Relapsed/refractory B-cell lymphoproliferative disorder	3	<i>Pneumocystis jirovecii</i> pneumonia
BCL-2 inhibitor (e.g. venetoclax)	CLL	1	<i>Aspergillus</i> spp., <i>Pneumocystis jirovecii</i> pneumonia
Hypomethylating agents (e.g. azacitadine)	MDS AML	5–13	Rates higher in relapsed/refractory disease versus its use as front-line therapy Rate of 13% when used in combination with BCL-2 inhibitor venetoclax <i>Aspergillus</i> spp., <i>Candida</i> spp.
FLT-3 inhibitors (e.g. midostaurin, gliteritinib)	AML	5	Limited data from clinical trial
Second generation IMiD, PI CD38 or SLAMF7 monoclonal antibodies	Relapsed/refractory myeloma	2–7	<i>Candida</i> spp., <i>Cryptococcus</i> spp.
CAR T-cell therapy	Relapsed/refractory ALL Relapsed/refractory NHL	5–8	In the setting of fluconazole or micafungin prophylaxis Rates up to 13% in patients with ALL <i>Aspergillus</i> spp., <i>Candida</i> spp., <i>Mucor</i> spp.
Bi-specific antibody therapies (e.g. blinatumomab)	Relapsed/refractory ALL Relapsed/refractory NHL	2	Limited clinical trial data

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; FLT-3, fms-like tyrosine kinase; IFD, invasive fungal disease; IMiD, immunomodulatory drug therapy; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PI, proteasome inhibitor; PI3K, phosphatidylinositol 3-kinase; SLAMF7, signalling lymphocytic activation molecule F7.

Q2. New evidence to support and guide the use of established prophylactic agents

Table 3 Summary of key new haematological treatments and recommended approaches to prophylaxis in adults and children

Therapy	Patient group	Infection	Measures	SoR	QoE
Targeted therapies (e.g. BTK inhibitors)	Relapsed/refractory B-cell lymphoproliferative disorders	Yeast and mould infections	Need for prophylaxis should be determined taking into account recent therapy (e.g. fludarabine-based), ongoing immune suppression and presence/absence of previous IFD	B	II
Immunomodulatory drug therapy, monoclonal antibody therapy (CD38/SLAMF7)	Relapsed/refractory myeloma	Yeast infection	Need for prophylaxis should be determined by number of previous lines of therapy, risk factors for IFD such as prolonged neutropenia and presence/absence of previous IFD	C	III
CAR T-cell therapy	Relapsed/refractory lymphoproliferative disorders	Yeast and mould infections	Yeast prophylaxis with fluconazole or micafungin Consider mould prophylaxis in the setting of prolonged neutropenia or additional treatments for high-grade cytokine release syndrome following CAR T-cell therapy Previous therapies including recent allogeneic or autologous HSCT should be taken into account	A	II
Bi-specific antibody therapies	ALL Being evaluated for other aggressive B-cell lymphoproliferative disorders	Yeast and mould infections	Need for prophylaxis should be determined taking into account recent therapy (e.g. fludarabine-based), ongoing immune suppression and presence/absence of previous IFD	C	III

ALL, acute lymphoblastic leukaemia; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease; QoE, quality of evidence; SLAMF7, signalling lymphocytic activation molecule F7; SoR, strength of recommendation.

Routine prophylaxis is not recommended, to consider on individual risk model.

CART, stem cell transplantation, previous history of IFD

Total isolates (2024)	15006
Fungi	1733
Yeast	1634
Mold	99

Q3. New options for antifungal prophylaxis

Table 4 Recommendations for choice and dose of antifungal prophylaxis agent in adults

Risk group		Antifungal agent	SoR	QoE	Comments
High risk	First line	Posaconazole Oral (tablets) Loading with 300 mg twice daily on Day 1, followed by 300 mg daily	A	I	Intravenous formulation can be used to continue prophylaxis if poor oral intake/absorption
	Alternate agents	Voriconazole Oral or intravenous 4 mg/kg twice daily†	A	II	High rates of adverse events (liver function abnormalities); variable CYP metabolism
		Micafungin Intravenous 100–150 mg daily	B	II	Could be used during periods of neutropenia if azoles contraindicated, poor oral intake/absorption
		Itraconazole Oral 200 mg twice daily	B	II	Less new data supporting its use compared to other azoles
		Liposomal amphotericin Intravenous 50–200 mg three times per week	B	II	Could be used if azoles contraindicated due to drug–drug interactions, adverse events, poor oral intake/absorption
		Isavuconazole Oral 200 mg three times per day for 48 h followed by 200 mg daily	C	II	Higher rates of IFD in cohort studies; could be used if other azoles contraindicated due to adverse events such as QTc prolongation
		Fluconazole Oral 200–400 mg daily	A	I	
		Echinocandin Intravenous Dosing dependent on agent	A	II	
		Itraconazole Oral 200 mg twice daily	A	II	
		No prophylaxis	B	II	
Low risk	First line	Fluconazole Oral 200–400 mg daily	A	I	
	Alternate agents	Echinocandin Intravenous Dosing dependent on agent	A	II	
Very low risk		Itraconazole Oral 200 mg twice daily	A	II	
		No prophylaxis	B	II	

†Dose used in prophylaxis studies have been 200 mg twice daily; measure voriconazole levels to ensure achievement of target level (refer to accompanying optimising antifungal therapy and TDM guidelines by Chau *et al.* 2021¹⁸², which can be found elsewhere in this supplement).

CYP, cytochrome P450; IFD, invasive fungal disease; QoE, quality of evidence; QTc, corrected QT interval; SoR, strength of recommendation.

IFD has emerged as a leading cause of infection related mortality among allo-SCT recipients over the past 2 decades.

Mold-active anti-fungal prophylaxis is recommended

1. Efficacy
2. Different pharmacokinetic
3. Drug-drug interaction
4. Toxicity profile

-> broad spectrum antifungal activity, favorable toxic profile

Q4. What critical drug-drug interactions should clinician be aware of and what is the need for TDM in the era of targeted and immune-based therapies

Dose adjustment of targeted therapies is required in major CYP3A4 interaction

Concomitant drug usage

Q5. How could antifungal prophylaxis recommendations be implemented into practice

Risk model

Local epidemiology , including incidence of IFD, pattern of fungal infection, rates of fungal resistance

Pharmacy cost and budgets

->Teamwork , to optimise the use of prophylaxis and diagnosis of breakthrough infection.