Epidemiology of invasive fungal disease in lymphoproliferative disorders

Invasive fungal disease (IFD) in the immunocompromised host is associated with high mortality,[1] prolonged stays in hospital and significant healthcare costs.[2] The epidemiology of IFD within the heterogeneous group of patients with lymphoproliferative disorders is not well defined and antifungal prophylaxis practices vary. In the current era of a myriad of novel therapeutic agents, we aim to describe the epidemiology of IFD and reflect upon prevention of IFD in this cohort of patients. To this end, we conducted a retrospective cohort study at the Peter MacCallum Cancer Centre (PMCC) to determine the epidemiology of IFD in patients with lymphoproliferative disorders receiving cytotoxic chemotherapy according to disease type and chemotherapy exposure.

For the period March 2009 to December 2011, all patients with lymphoproliferative neoplasms who received mold-active antifungal therapy were retrospectively identified from the antimicrobial stewardship system (Guidance MS, Melbourne Health) and pharmacy dispensing system. Mold-active therapy was defined as treatment with a polyene, echinocandin or mold-active triazole (i.e. posaconazole or voriconazole). Clinical, microbiological and radiological records were reviewed to capture patients' demographics, underlying lymphoproliferative disorder by type and stage, chemotherapy type and schedule, antifungal prophylaxis status, type and site of IFD, antifungal treatment received and clinical outcomes. In order to identify all patients undergoing treatment for lymphoproliferative neoplasms during the study period, diagnoses and treatment duration were extracted from the chemotherapy administration system (CHARM). Oral cytotoxic agents such as fludarabine and oral immunomodulatory drugs (lenalidomide, thalidomide) and/or proteasome inhibitors (bortezomib) were identified from the pharmacy dispensing system.

Patients received antifungal prophylaxis in accordance with the Australian national consensus guidelines for antifungal prophylaxis.[3] In patients deemed at high risk of IFD without an approved indication, antifungal prophylaxis was used at the discretion of the treating clinician in consultation with the infectious diseases department. In patients suspected of having an IFD because of clinical symptoms or persistent fever, the diagnostic work-up typically included imaging with high-resolution computed tomography (CT) of the chest and sinuses (if symptoms) or fluorine-18 fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT), followed by directed tissue sampling for microscopy and fungal culture. Molecular testing with Aspergillus polymerase chain reaction (PCR) and galactomannan testing on serum and bronchoalveolar lavage (BAL) fluid were routinely performed.[4] The optical index cutoff for a positive galactomannan test was 0.5 on serum and 1.0 on BAL.[4,5]

IFD was defined and classified according to the European Organisation for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria.[6] Lymphoproliferative disorders were classified according to consensus definitions[7] into seven categories: precursor lymphoid neoplasms; mature B-cell neoplasms - chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), plasma cell neoplasms, other B-cell non-Hodgkin lymphoma; mature T- and NK-cell neoplasms; and Hodgkin lymphoma. Prevalence of infections was defined as the number of patients with IFD expressed as a proportion of the total number of treated patients for each category during the study period. As a novel means of determining the effect of treatment intensity on IFD risk within each category, the rate of IFD was expressed as number of IFD cases per 10,000 treatment days. Treatment days were calculated from the first to the last day of chemotherapy administered to patients within each category during the study period. Outcomes of IFD treatment were evaluated at 30 days. The study was approved by the PMCC Human Research Ethics Committee.

During the study period, 773 patients fulfilled the inclusion criteria. Overall, 29 episodes of IFD were identified in 29 patients, corresponding to an IFD prevalence of 3.8% [95% confidence interval (CI) 2.5-5.4%]. Patients with IFD had a mean age (range) of 62 years (18-88 years) and a male predominance (65%). IFD were classified as proven in ten cases, probable in eight, and possible in 11.

Table 1. Characteristics of studied patients with lymphoproliferative disorders (2009-2011).

	Hematologic malignancy						
	Precursor lymphoid neoplasms	Mature B-cell neoplasms				Mature T- & NK-cell neoplasms	Hodgkin lymphoma
		CLL/SLL	DLBCL	Plasma cell neoplasms	Other B-cell NHL		
Total n. of patients	17	51	186	251	175	37	56
N. receiving antifungal prophylaxis							
Fluconazole	7	9	99	103	38	18	13
Mold-active agent	9	3	6	6	7	3	0
IFD episodes							
Number	5	4	8	7	3	0	2
IFD prevalence (95% CI)	29.4% (9.5-68.6%)	7.8% (2.1-20.1%)	4.3% (1.9-8.5%)	2.8% (1.1-5.7%)	1.7% (0.4-5.1%)	0%	3.6% (0.4-12.9%)
IFD rate per 10,000 treatment days	10.7	4.4	2.8	*	0.4	0	2.8

*CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; *Given requirement for continuous oral chemotherapy in myeloma cohort, IFD rate per 10,000 treatment days not provided.*

Table 2. Characteristics of patients with lymphoproliferative disorders with invasive fungal disease (2009-2011).

Case	Age sex	Malignancy, disease status	Previous treatments	Treatment prior to IFD (Timing of IFD)	Antifungal prophylaxis prior to IFD	EORTC/MSG	Prolonged neutropenia[a]	High dose steroid[b]	Clinical presentation	Site of infection	Diagnostic investigations	Treatment	Outcome
Precursor lymphoid neoplasms													
1	54M	ALL (B-cell), New diagnosis	N	CODOX-M (C1,D25)	Fluconazole	Proven	N	N	Severe sepsis, respiratory failure requiring intubation	Lung	Bronchial tissue culture: *Aspergillus fumigatus*	Caspofungin and liposomal amphotericin	Sepsis multi-organ, failure
2	30M	ALL (T-cell), Disease progression	HyperCVAD POMP FLAG/Ida/ L-asparaginase	Neralabine (C1, D8)	Fluconazole	Proven	Y	Y	Persistent fevers, hemorrhage from mycotic aneurysm	Vascular invasion (fungal elements seen on arterial wall)	Artery tissue culture negative, Galactomanan positive	Liposomal amphotericin	Palliated, Died from relapsed disease and infection
3	31M	ALL (T-cell), Remission	Induction regimen unknown AlloSCT (2008) GVHD-gut	N	N	Proven	N	Y	Chronic nephrocolic fistula , L) nephrectomy & colonic resection	Tissue/organ invasion	Fungal microscopy: hyphae seen, culture negative (fungal elements suggestive of mucor seen on tissue)	Posaconazole	Alive at 30 days
4	43F	ALL (Pre-T cell), New diagnosis	HyperCVAD L-asparaginase HiDAC	Peg asparaginase (C2 D8)	Posaconazole	Possible	Y	N	Febrile neutropenia	Lung HRCT: R) upper lobe fungal mycetoma	BAL not done	Posaconazole	Alive at 30days
5	56F	ALL (Pre-B cell), Remission	HyperCVAD Methotrexate/ L-asparaginase	Cyclo/TBI conditioned alloSCT (D+186)	Fluconazole	Possible	N	N	Respiratory symptoms, Pulmonary GVHD on cyclophosphamide/ low dose prednisolone	Lung HRCT: nodules with patchy ground glass changes	BAL: culture negative, Asp PCR positive	Posaconazole	Alive at 30 days
Mature B-cell neoplasms													
6	69M	SLL/CLL Disease progression	FC-R R-CHEP Ofatumumab R-CEP	N	N	Proven	N	N	Headache, confusion	CNS	CSF culture: *Cryptococcal neoformans*	Liposomal amphotericin/ flucytosine followed by fluconazole	Alive at 30 days
7	71F	SLL/CLL Disease progression	Fludarabine/ cyclo/ oblimersen (Genasense®)	N	N	Proven	N	N	Fever, groin cellulitis	Disseminated	Blood culture: *Candida glabrata*	Caspofungin followed by Voriconazole	Alive at 30 days
8	77M	SLL/CLL Relapse	Chlorambucil FC-R	VAD (C1 D13)	N	Probable	N	Y	Fevers, hypoxia	Lung	BAL: *A. fumigatus*	Posaconazole	Alive at 30 days
9	70M	SLL/CLL Disease progression	FC-R	R-CEP (C1 D10)	N	Possible	N	Y	Febrile neutropenia, respiratory symptoms	Lung	BAL: *Stenotrophomonas sp.* and *Candida sp.*	Voriconazole	Died due to respiratory failure
10	63F	DLBCL *De novo,* Partial response	R-CHOP+IT methotrexate R-VIC	Stanford BCNU autoSCT (D+6)	Fluconazole	Proven	Y	Y	Sepsis, respiratory failure	Disseminated	Blood culture and BAL culture: *Candida dubliniensis*	Caspofungin	Alive at 30 days
11	55F	DLBCL Large cell transformation from follicular lymphoma, Disease progression	R-CHOP RVIC Stanford BCNU autoSCT Rituximab	FC- R (C6 D99)	N	Probable	N	Y	Fevers, dyspnea	Lung	BAL: no growth, Asp PCR positive Sputum culture: *A. fumigatus*	Voriconazole	Died from multiorgan failure
12	60M	DLBCL *De novo,* Complete metabolic response	R-CHOP Doxorubicin R-VIC+IT methotrexate	Stanford BCNU autoSCT (D+12)	Fluconazole	Probable	Y	Y	Febrile neutropenia, *Streptococcus pneumoniae* bacteremia	Lung	BAL not done Sputum culture: *A. fumigatus*	Voriconazole	Alive at 30 days

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13	51M	DLBCL *De novo,* Relapse	R-CHOP MADEC autoSCT FC-R alloSCT ICE RCHOP+radiotherapy Marizomib (proteasome inhibitor) trial	R-VIC (C1 D13)	N	Possible	Y	N	Fevers, *Staphylococcus aureus* endocarditis, bowel obstruction	Lung HRCT: bilateral parenchymal nodules	BAL not done (due to patient frailty)	Voriconazole	Died from multiorgan failure
14	74F	DLBCL *De novo,* Primary refractory	R-CHEP	Gemcitabine/ venorelbine (C4 D147)	N	Possible	N	Y	Fevers, respiratory symptoms	Lung HRCT: bilateral nodules	BAL not done	Voriconazole	Alive at 30 days
15	72M	DLBCL Large cell transformation from SLL/CLL	CVP RCHOP+ radiotherapy	HyperCVAD (C1A D29)	Fluconazole	Possible	N	Y	Febrile neutropenia, R) endobronchial lesion	Lung	BAL: culture negative, Asp PCR positive	Voriconazole	Alive at 30 days
16	53M	DLBCL Large cell transformation from SLL/CLL	FC conditioned alloSCT Mild buccal GVHD	R-CHOP (C3 D37)	Posaconazole	Possible	Y	Y	Fevers, pancytopenia	Lung HRCT: bilateral scattered nodules	BAL not done Serum Asp PCR positive	Voriconazole	Died from multiorgan failure
17	72M	DLBCL Large cell transformation from SLL/CLL	Chlorambucil/ fludarabine/ cyclo FC-R R-CVP	R-CVP (C1 D8)	Fluconazole	Possible	N	N	Fevers, L)pleural effusion	Lung HRCT: R) lower lobe nodule, increasing in size	BAL not done; serum Asp PCR positive	Voriconazole	Died from malignancy
18	62F	Myeloma, Disease progression	AD Depsipeptide/ bortez autoSCT Cyclo/dex/len	DTPACE (C1 D16)	Fluconazole	Proven	Y	Y	Febrile neutropenia	Sinus	Blood culture: *Scedosporium prolificans*	Liposomal amphotericin	Died from disseminated infection
19	69M	Myeloma, Disease progression	VAD Thal Bortez/dex Cyclo/Len/dex	Melphalan AutoSCT (D+15)	Fluconazole	Proven	Y	Y	Febrile neutropenia	Disseminated	Blood culture: *Candida parapsilosis*	Caspofungin followed by Voriconazole	Alive at 30 days
20	59M	Myeloma, Disease progression	autoSCT Thal Bortez Len Marizomib (NP10052)	Bortez/ romidepsin (C3 D29)	N	Proven	N	N	Fevers, respiratory failure, influenza A infection	Disseminated	Blood culture: *Candida albicans*	Caspofungin	Died from respiratory failure
21	64F	Myeloma, Disease progression	VAD autoSCT Bortez/romidepsin	DVPACE (C1 D13)	Fluconazole	Probable	Y	Y	Fevers, respiratory symptoms	Lung	BAL culture: *Scopulariopsis* sp.	Caspofungin and Voriconazole	Died from respiratory failure
22	33F	Myeloma, Relapse	AD Bortez/ romidepsin autoSCT Len/cyclo D-PACE autoSCT DT-PACE	Melphalan AutoSCT (D+13)	Fluconazole	Probable	Y	N	Febrile neutropenia	Lung HRCT: R) nodule and consolidation	BAL culture: *A. fumigatus*	Voriconazole followed by posaconazole	Alive at 30 days
23	64M	Myeloma, Disease progression	AD Dex/thal autoSCT cyclo/len/dex cyclo autoSCT	Cyclo/ bortezomib (C1 D12)	N	Possible	Y	N	Fevers	Lung HRCT: bilateral upper lobe nodules	BAL: culture negative	Voriconazole	Alive at 30 days
24	59F	Myeloma, New diagnosis	N	Len/dex	N	Possible	Y	Y	Fevers, respiratory symptoms	Lung HRCT: cavitating nodules	BAL: culture negative, Asp PCR positive	Voriconazole	Alive at 30 days

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25	86M	Other B- cell NHL, follicular lymphoma New diagnosis	N	R-CEP (C1 D23)	N	Probable	N	N	Fevers, respiratory symptoms, lower limb venous thrombosis, urosepsis	Lung	BAL not done, Sputum culture: *A. fumigatus*	Voriconazole	Died from multiorgan failure
26	52M	Other B- cell NHL, Burkitt-like lymphoma, Refractory disease	CODOX-M/IVAC R-CHOP	FLAG/L-Asparaginase/ TBI conditioned autoSCT (D+14)	Fluconazole	Probable	Y	N	Fevers, respiratory symptoms	Lung	BAL culture: *Aspergillus terreus*	Voriconazole	Died from refractory disease
27	68M	Other B-cell NHL, follicular lymphoma Remission	Chlorambucil CVP Cyclo/prednisolone Fludarabine/ mitoxantrone ESHAP autoSCT	FC-R (C6 D298)	Fluconazole	Probable	N	Y	Fevers, respiratory failure	Lung	BAL culture: *A. fumigatus*	Voriconazole	Alive at 30 days
Hodgkin Lymphoma													
28	18F	Hodgkin lymphoma, Relapse	COG-AHOD0031 protocol IGEVx4 BEAM conditioned autoSCT	VIC (4 months post C3)	N	Proven	Y	N	Sepsis	Disseminated	*Candida parapsilosis*	Fluconazole	Alive at 30 days
29	24M	Hodgkin lymphoma, Relapse	ABVD and radiotherapy VIC BEAM	Stanford BCNU autoSCT (D+37)	Fluconazole	Possible	Y	N	Dyspnea	Lung HRCT: features of angioinvasion	BAL not done	Voriconazole	Alive at 30 days

[a]*Neutropenia (PMN <500/mm³) for >10 days before date of IFD;* [b]*Prednisolone equivalents >20 mg per day for >1 month. IFD: invasive fungal disease; EORTC: European Organisation for Research and Treatment of Cancer; MSG: Mycology Study Group; Y: Yes; N: No; ALL: acute lymphoblastic lymphoma; SLL: small lymphocytic leukemia; CLL: chronic lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; autoSCT: autologous stem cell transplant; alloSCT: allogeneic stem cell transplant; GVHD: graft-*versus*-host-disease; HRCT: high resolution computed tomography; BAL: bronchoalveolar-lavage; Asp PCR: Aspergillus polymerase chain reaction; N/A: not applicable; CODOX-M: cyclophosphamide-vincristine-doxorubicin-methotrexate; IVAC: ifosfamide-etoposide-cytarabine; HyperCVAD Part A:cyclophospamide-vincristine-doxorubicin-cytarabine-dexamethasone; HyperCVAD Part B: methotrexate(intravenous and intrathecal)-cytarabine(intrathecal); Hidac: high dose cytarabine; POMP: mercaptopurine-vincristine-methotrexate-prednisolone; FLAG: fludarabine-cytarabine-filgrastim; Ida: Idarubicin; cyclo: cyclophosphamide; TBI: total body irradiation; FC: fludarabine-cyclophosphamide-rituximab; CHOP: cyclophosphamide-doxorubicin-vincristine-prednisolone; R: rituximab; CEP: cyclophosphamide-etoposide-prednisolone; VAD: vincristine-doxorubicin-dexamethasone; VIC: etoposide-ifosfamide-carboplatin; Stanford BCNU: carmustine-etoposide-cyclophosphamide ; MADEC: cytosine arabinoside-etoposide-methotrexate-cyclophosphamide-dexamethasone; ICE: idarubicin-cytarabine-etoposide; CVP:cyclophosphamide/vincristine/prednisolone; AD: doxorubicin-dexamethasone; VAD: vincristine-doxorubicin-dexamethasone; bortez: bortezomib; dex: dexamethasone; thal: thalidomide; len: lenalidomide; DTPACE: dexamethasone-thalidomide-cisplatin-doxorubicin-cyclophosphamide-etoposide; DVPACE: dexamethasone-bortezomib-cisplatin-doxorubicin-cyclophosphamide-etoposide; ESHAP: etoposide-methylprednisolone-cytarabine-cisplatin; COG-AHOD0031 protocol (trial): doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide with or without dexamethasone, etoposide, cytarabine, cisplatin, and/or radiotherapy; IGEV: ifosfamide-gemcitabine-vinorelbine; BEAM: carmustine-etoposide-cytarabine-melphalan; ABVD: doxorubicin-bleomycin-vinblastine-dacarbazine.*

Fluconazole and mold-active antifungal prophylaxis were administered to 287/773 (37.1%) and 38/773 (4.9%) patients, respectively.

Patients with precursor lymphoid neoplasms had the highest prevalence of IFD (5/17; 29.4%, 95% CI 9.5-68.6%), followed by patients with mature B-cell neoplasms-CLL/SLL (4/51; 7.8%, 95% CI 2.1-20.1%), DLBCL (8/186; 4.3%, 95% CI 1.9-8.5%) and plasma cell neoplasms (7/251; 2.8%, 95% CI 1.1-5.7%). IFD events per treatment days demonstrated a similarly larger relative burden of disease in patients with precursor lymphoid neoplasms (10.7 IFD per 10,000 treatment days) (Table 1). Mold-active antifungal prophylaxis was used in 52.9% of patients with precursor lymphoid neoplasms. Of the five patients with precursor lymphoid neoplasms who developed IFD, three had received fluconazole prophylaxis, one had received posaconazole prophylaxis and one received no antifungal prophylaxis. IFD was observed to occur at different treatment stages of disease, and these are summarized in Table 2.

Aspergillus species was the most frequently identified fungal pathogen (13 cases) (cultured in 7 cases; detected on PCR in 8 cases). Other fungal pathogens, in order of reducing frequency included *Candida* (5 cases), *Scedosporium* (1 case), *Scopulariopsis* (1 case) and *Cryptococcus* (1 case) species. The pulmonary system (19 cases) was the most common site of IFD, followed by blood (5 cases), sinus (2 cases), soft tissue/viscera (2 cases) and central nervous system (1 case). Of the 29 patients treated for IFD, 12 (41.4%) required admission to the intensive care unit and 30-day all-cause mortality was 31.0% (9/29).

IFD is an important and potentially modifiable cause of morbidity and mortality in patients with lymphoproliferative disorders receiving chemotherapy. Few studies have described the epidemiology and treatment outcome of IFD in these patients and none has incorporated all of the current diagnostic strategies available (e.g. *Aspergillus* PCR, galactomannan and FDG PET/CT diagnostics). Our study identified an overall IFD prevalence of 3.8% with cases occurring in all disease subsets except mature T- and NK-cell lymphoma. The prevalence of IFD was highest in patients with precursor lymphoid neoplasms (29.4%). This occurred despite 52.9% of patients receiving mold-active prophylaxis. This finding is consistent with a 28% incidence reported at another Australian center[8] and may be attributed to the increasing intensity of induction chemotherapy protocols for lymphoblastic

lymphoma comprising high corticosteroid exposure and prolonged periods of neutropenia. Use of antifungal prophylaxis in this cohort is challenging given the potential for drug interactions with vinca alkaloids.[8] Triazole antifungal drugs potentiate vincristine-related neuropathy and although antifungal prophylaxis is sometimes administered intermittently or withheld during vincristine-containing treatment, this approach is complicated by the variable half-lives of these agents.[9]

The observed higher frequency of IFD in patients with lymphoblastic lymphoma argues for new approaches to the prevention of IFD in this group of patients, including a reappraisal of polyene and echinocandin prophylaxis. An alternative approach to mitigating the clinical consequence of IFD would be routine enhanced surveillance with a combination of Aspergillus PCR and galactomannan testing as has been evaluated in allogeneic stem cell recipients.[10] We did not observe a well-defined high-risk period for IFD in our patients - some IFD cases were diagnosed during induction chemotherapy and others during treatment for progressive or relapsed disease - making a targeted surveillance approach more challenging.

IFD occurred at a lower rate in patients with CLL/SLL (7.8%), DLBCL (4.3%) and plasma cell neoplasms (2.8%). Various studies have found invasive mold infection complicating alemtuzumab treatment in patients with CLL/SLL, most likely due to the combination of humoral immunodepletion inherent to the disease and treatment-related immunosuppression.[11] In patients with myeloma, IFD has been observed to occur during disease progression and following a median of five lines of prior treatment.[12] While there are some reports of IFD rates in the other lymphoproliferative disorders, there are no studies to date quantifying the burden of disease and role of antifungal prophylaxis in these patients. Consistent with findings in other groups of immunocompromised patients, Aspergillus and Candida were the most frequent IFD pathogens in our cohort. Overall, we observed a 30-day all-cause mortality of 31.0% and this is consistent with previous studies.[8] There is a possibility that IFD diagnoses are delayed in these patients as they lie outside traditional risk groups due to uncertainty surrounding IFD risk, the paucity of data on IFD epidemiology and absence of standardized antifungal prophylaxis recommendations amid evolving disease treatments.

Study limitations include the retrospective nature of the study, and the fact that it was undertaken in a quaternary referral center. Our IFD prevalence may be an underestimate as cases were defined on the basis of receipt of antifungal agents; however, patients at this center are more likely to be pretreated and therefore at higher risk.

In summary, we observed significant mortality in patients with IFD complicating lymphoproliferative disorders, and identified patients with precursor lymphoid neoplasms as the subgroup at highest risk. The increasing age-standardized incidence of lymphoproliferative disorders in the aging population receiving chemotherapy means that the burden of IFD is anticipated to increase over time. Larger, multicentre, prospective, surveillance studies are, therefore, required to quantify IFD risk and to test strategies for early detection and/or prevention.

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