Invasive fungal infections in patients with multiple myeloma: a multi-center study in the era of novel myeloma therapies

Multiple myeloma (MM) is a hematologic malignancy with increasing prevalence in older populations.[1] Infections, particularly pyogenic infections and reactivation of latent viral infections,[2] are a leading cause of morbidity and mortality in patients with MM. Previously, invasive aspergillosis (IA) had been found to be a significant opportunistic infection in patients with myeloma managed with intensive conventional combination chemotherapeutic regimens with nearly 50% attributable mortality. IA tended to occur early in the treatment course in patients with higher disease stage.[3] However, the treatment of myeloma has undergone a paradigm shift with the use of immunomodulatory drugs (IMiDs), proteasome inhibitors (PI) and autologous hematopoietic stem cell transplant (ASCT) as the new standard of care.

The epidemiology and outcomes of invasive fungal infections (IFI) are well defined in other hematology populations, and are supported by guidelines for antifungal prophylaxis.[4] However, the disease burden and characteristics of IFI in patients with MM in the era of novel agents have not been previously reported. In addition, the contribution and impact of these novel agents and early use of ASCT on risk of IFI is uncertain. Therefore, our study aimed to define the role of antifungal prophylaxis, the epidemiology, risk factors and outcomes of IFI in patients with MM receiving novel agents.

The study was conducted at the Peter MacCallum Cancer Centre (PMCC) and Austin Hospital (AH) which are tertiary referral centers for MM in Victoria, Australia. All patients with MM and an IFI managed at both centers from January 2009 to December 2011 were identified retrospectively from electronic medical management and discharge records, antimicrobial restricted approval and pharmacy dispensing systems and included in this study. Clinical, microbiology and radiology records of the identified patients were further reviewed using a standardized tool to capture the following: patient demographics, myeloma type, stage and treatment received (number of treatment cycles, lines of therapy), known predispositions for IFI (neutropenia, receipt of corticosteroids or chemotherapy), use of antifungal prophylaxis, clinical features, type and site of IFI, antifungal treatment received and outcomes (need for intensive care management and all-cause mortality at 30 days).

During the study period, patients with MM received treatment consistent with prevailing international practices including the use of IMiDs, (lenalidomide or thalidomide) and/or PI (bortezomib) in combination with corticosteroids. Fluconazole prophylaxis was routinely used for the period of ASCT (up to 3 months post transplant) for all patients at PMCC and in patients with past and/or expected history of mucositis at AH during the period of neutropenia. Patients suspected of having an IFI or with persistent febrile neutropenia with unclear source were investigated with high-resolution computer tomography (CT) of the chest and sinuses or position emission tomography-CT scan followed by directed tissue sampling for microscopy and fungal culture. Molecular testing with Aspergillus polymerase chain reaction and galactomannan testing on serum and BAL were routinely used at PMCC. A line of therapy as defined by the International Myeloma Workshop consensus panel recommendations was used to provide an estimate of disease burden, treatment and number of relapses.[5] IFI was defined and classified according to the European Organisation for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria.[6] We received approval from human research ethics committees at both institutions.

Table 1. Overall characteristics of patients with myeloma (2009 to 2011).

Patients' characteristics	Overall n=372 (%)	PMCC n=251 (%)	AH n=121 (%)
Age (median; IQR): years	65 (58-72)	64 (56 -71)	67 (59-75)
Gender:			
Male	226 (61)	148 (59)	78 (64)
Female	146 (39)	103 (41)	43 (36)
Treatment received:			
Immunomodulatory drug	316 (85)	225 (90)	91(75)
Bortezomib	93 (25)	63 (25)	30 (25)
ASCT	135 (36)	101 (40)	34 (28)
Anti-fungal prophylaxis:			
Fluconazole	118 (32)	103 (41)	15 (12)
Mold active agent[#]	6* (2)	6 (2)	0 (0)
Invasive fungal infection:	n = 9 (%)	n = 7 (%)	n = 2 (%)
Proven	3 (33)	3 (43)	0 (0)
Probable	2 (22)	2 (29)	0 (0)
Possible	4 (44)	2 (29)	2 (100)

*PMCC: Peter MacCallum Cancer Centre; AH: Austin Hospital. [#]Mold active agents include voriconazole, posaconazole and liposomal amphotericin. *Of the 6 patients who received mold active antifungal prophylaxis, 2 received posaconazole following allogeneic stem cell transplant and 4 received mold-active agent (voriconazole, posaconazole) due to previous isolation of Aspergillus sp. in sputum and multiple lines of previous therapy (median = 3).*

Overall 372 patients received treatment for MM at both centers and were followed for a median of 24 months. Nine patients (2.4%) were diagnosed with 9 episodes of IFI: 3 were proven, 2 probable and 4 possible according to EORTC/MSG criteria. Rates of invasive mold infection and IA were 0.8% (3 of 372) and 0.3% (1 of 372), respectively. The IFI rate was 2.2% (3 of 135) following ASCT and 2.5% (6 of 237) for patients who had not received an ASCT. The rate of IFI in patients who received 3 lines or more of therapy was 15.0%. Patients' characteristics are shown in Table 1.

Patients with an IFI had a median age of 62 (IQR, 59-64) years and were predominantly male (6 of 9). A majority of patients (6 of 9) were International Staging System stage 1 at myeloma diagnosis. Most IFI episodes (8 of 9) occurred with myeloma progression (n=5) or after a second or third autograft (n=3) at a median of 35 (26-60) months following initial disease diagnosis after having received a median of 5 lines of therapy. Predisposing factors for IFI were present in the majority of instances: neutropenia less than $0.5x10^9/L$ for ten days or more temporally related to onset of an IFI (8 of 9 cases), corticosteroid therapy (≥0.5 mg/kg/day of prednisolone equivalent over 4 weeks in 3 of 9), and T-cell suppressive chemotherapy prior to diagnosis of IFI (6 of 9).

The sites of involvement were pulmonary (6 of 9) and disseminated (3 of 9). Isolated fungal pathogens included *Candida albicans, Candida parapsilosis, Scedosporium prolificans* (proven), *Aspergillus fumigatus*, and *Scopulariopsis sp.* (probable). All patients with an IFI received antifungal treatment. The majority of episodes 5 of 9 (55.6%) (2 proven, one probable and 2 possible) required management in the intensive care unit and overall 30-day all-cause mortality was (4 of 9) 44.4%. Characteristics of IFI episodes and

outcomes are summarized in Table 2. Univariate and multivariate regression analysis of risk factors was performed using IFI as the evaluable outcome. Univariate analysis demonstrated that receipt of bortezomib (P=0.01) and 3 or more lines of therapy for MM (P<0.01) were associated with IFI (Table 3). Multivariate logistic regression analysis demonstrated that receipt of 3 or more lines of therapy within three years was independently associated with an increased risk of IFI (P=0.02) (Table 3).

In our study, we observed an overall low IFI rate of 2.4% with an invasive mold infection rate of 0.8%. Despite the lack of use of mold-active prophylaxis (2%), the rates of invasive mold infection and IA in this study (0.8% and 0.3%, respectively) are comparable to rates reported in other studies of MM patients during the last decade (0.5%-0.7%).[7,8] The use of fluconazole prophylaxis in the study was consistent with Australian antifungal guidelines.[4] In this context, our IFI rate of 2.2% following ASCT remains within the anticipated range expected following ASCT for patients with other hematologic malignancies.[9,10] The uptake of a diagnostic driven approach to persistent neutropenic fever following ASCT does not appear to have led

Table 2. Clinical features and outcomes of patients with myeloma and an invasive fungal infection.

Pt. n.	Disease status	N. of lines of therapy	Treatment regimen prior to IFI	AF prophylaxis prior to IFI	EORTC/ MSG	Prolonged neutropenia	High-dose steroids	Clinical presentation	Site of infection	Microbiology Results	Treatment	Outcome
1	Progression	6	DTPACE	Fluconazole	Proven	Yes	Yes	Febrile neutropenia	Sinus	Blood culture: *Scedosporium prolificans*	Liposomal amphotericin	Death from disseminated infection
2	Progression	5	Melphalan	Fluconazole	Proven	Yes	No	Febrile neutropenia following second ASCT for progressive disease	Not applicable	Blood culture: *Candida parapsilosis*	Caspofungin followed by voriconazole	Survived past 30 days
3	Progression	5	Bortez and romi	None	Proven	No	No	Persistent fevers Respiratory failure from concurrent influenza A infection	Not applicable	Blood culture: *Candida albicans*	Caspofungin	Death from respiratory failure
4	Progression	3	DVPACE	Fluconazole	Probable	Yes	Yes	Persistent fever Respiratory symptoms	Chest	BAL: *Scopulariopsis sp.*	Caspofungin and voriconazole	Death from respiratory failure
5	Progression	6	Melphalan	Fluconazole	Probable	Yes	No	Persistent fever Respiratory symptoms following third ASCT for progressive disease	Chest	BAL: *Aspergillus fumigatus*	Voriconazole followed by posaconazole	Survived past 30 days
6	Progression	5	Cyclop and bortez	None	Possible	Yes	No	Persistent febrile neutropenia	HRCT: nodules in upper lobe	BAL: Culture negative	Voriconazole	Survived past 30 days
7	Induction	1	Len and dex	None	Possible	Yes	Yes	Febrile neutropenia Respiratory symptoms	HRCT: multiple cavitatory nodules	BAL: Culture negative; Aspergillus PCR positive	Voriconazole	Survived past 30 days
8	Progression	4	Melphalan	None	Possible	Yes	No	Febrile neutropenia following second ASCT for progressive disease	HRCT: Right middle lobe nodules	BAL: Culture negative	Posaconazole	Survived past 30 days
9	Progression	2	Len	None	Possible	Yes	No	Febrile with evolving skin lesions for investigation	HRCT: multiple scattered nodules	BAL: Culture negative	Posaconazole followed by liposomal amphotericin	Death from disseminated bacterial infection

AF: antifungal; IFI: invasive fungal infection; EORTC: European Organization for Research and Ttreatment of Cancer; MSG: Mycology Study Group; ASCT: autologous hematopoietic stem cell transplantation; HRCT: high-resolution computer tomography; BAL: broncho-alveolar lavage DTPACE: dexamethasone-thalidomide-cisplatin-doxorubicin-cyclophosphamide and etoposide; DVPACE: dexamethasone-bortezomib-cisplatin-doxorubicin-cyclophosphamide and etoposide; Bortez and romi: bortezomib and romidepsin; cyclo: cyclophosphamide; len and dex: lenalidomide and dexamethasone.

Table 3. Impact of multiple myeloma treatment factors on risk of developing invasive fungal infection.

Variable	Univariate				Multivariate*	
	Number with an IFI	Number of patients	OR (95% CI)	P	OR (95% CI)	P
Age ≤ 65 years	7	188	3.48	0.12	2.60	0.25
Age > 65 years	2	184	(0.71-16.98)		(0.50-13.48)	
Receipt of AF prophylaxis	4	122	1.66	0.46		
No AF prophylaxis	5	250	(0.44-6.30)			
< 3 lines of therapy	3	332	19.35	<0.01	15.08	0.02
≥ 3 lines of therapy	6	40	(4.63-80.88)		(1.64-138.30)	
ASCT	3	135	1.13	0.87		
No ASCT	6	237	(0.28-4.59)			
Received bortezomib	6	93	6.34	0.01	0.93	0.95
No bortezomib	3	279	(1.55-25.90)		(0.10-8.77)	
< 10 cycles of treatment	3	235	3.54	0.08	1.88	0.42
≥ 10 cycles of treatment	6	137	(0.87-14.39)		(0.41-8.68)	

*IFI: invasive fungal infection; OR: odds ratio; CI: confidence interval; AF: anti-fungal; ASCT: autologous hematopoietic stem cell transplant. *Covariates were included in the model if univariate analysis demonstrated P<0.20. All analyses were performed using Stata (v.9.0, StataCorp Inc., Texas, USA) and P≤0.05 was considered statistically significant.*

to a higher IA rate through increased detection in our study in comparison to other centers using a similar approach.[11]

We observed that IFI occurred mostly during the period of disease progression (85.7%) with a median of 35 months between initial myeloma diagnosis and an episode of IFI and a median of 5 lines of treatment. This is in contrast to older studies where a much earlier onset of IFI had been reported.[3,8] This shift could be because IMiDs and PI are inherently less myelosuppressive compared with conventional chemotherapy which now tends to be used in combination for patients with refractory or progressive disease.[12] Cumulative deficits in various arms of the immune system, in particular of cell-mediated immunity due to progressive disease, could also account for our findings.[2]

The impact of novel agents and use of ASCT on risk of IFI has not been previously evaluated. In our study, the type of treatment, including receipt of ASCT and bortezomib did not appear to be independently associated with risk of developing an IFI. However, the number of lines of therapy was significantly associated with an increased risk of developing an IFI. With 3 or more lines of therapy, the IFI rate was 15.0%, which would warrant consideration of antifungal prophylaxis or surveillance. This finding suggests cumulative exposure to immunosuppressive treatment and disease burden is a greater determinant of IFI risk than type of individual therapy.

Mortality rates of up to 60% were reported in the earlier era of conventional therapy.[3] IFI in our patients was still associated with significant morbidity and mortality with nearly 60% of episodes requiring ICU management and a 30-day all-cause mortality rate of 44%. These outcomes underscore the need for improvement in early diagnosis and treatment.

Our study has several limitations. Intensity of diagnostic evaluation for IFI was determined by the treating physician, which may have resulted in selection bias favoring diagnosis of IFI in symptomatic and unwell patients. Although the number of detected cases of IFI was limited, these were drawn from a large heterogeneously treated myeloma patient population and our data have allowed us to define the relationship between antifungal prophylaxis, IFI and outcomes.

In our dedicated study of IFI in patients with MM, the first in the era of novel anti-myeloma agents, rates of IFI and IA, including following ASCT, remain low. This is in the context of fluconazole prophylaxis during ASCT, overall low use of mold-active prophylaxis and diagnostic driven strategies for neutropenic fever. It appears cumulative treatment exposure and disease burden (≥ 3 lines of therapy in 3 years) is a greater determinant of IFI risk than type of individual therapy. Therefore, a high-risk group has been identified which could benefit from mold-active prophylaxis or enhanced surveillance for IFI.

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References

1. Turesson I, Velez R, Kristinsson SY, Landgren O, editors. Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. Mayo Clin Proc; 2010: Elsevier.
2. Teh BW, Harrison SJ, Pellegrini M, Thursky KA, Worth LJ, Slavin MA. Changing treatment paradigms for patients with plasma cell myeloma: impact upon immune determinants of infection. Blood Rev. 2014;28(2):75-86.

3. Lortholary O, Ascioglu S, Moreau P, Herbrecht R, Marinus A, Casassus P, et al. Invasive aspergillosis as an opportunistic infection in nonallografted patients with multiple myeloma: a European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the Intergroupe Francais du Myelome. Clin Infect Dis. 2000;30(1):41-6.
4. Slavin MA, Heath CH, Thursky KA, Morrissey CO, Szer J, Ling LM, et al. Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy. Intern Med J. 2008;38(6b):468-76.
5. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-5.
6. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813-21.
7. Nosari AM, Pioltelli ML, Riva M, Marbello L, Nichelatti M, Greco A, et al. Invasive fungal infections in lymphoproliferative disorders: a monocentric retrospective experience. Leuk Lymphoma. 2014;55(8):1844-8.
8. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 2006;91(8):1068-75.
9. Cornet M, Fleury L, Maslo C, Bernard JF, Brucker G, Invasive Aspergillosis Surveillance Network of the Assistance Publique-Hopitaux de P. Epidemiology of invasive aspergillosis in France: a six-year multicentric survey in the Greater Paris area. J Hosp Infect. 2002;51(4):288-96.
10. Jantunen E, Salonen J, Juvonen E, Koivunen E, Siitonen T, Lehtinen T, et al. Invasive fungal infections in autologous stem cell transplant recipients: a nation-wide study of 1188 transplanted patients. Eur J Haematol. 2004;73(3):174-8.
11. Gil L, Kozlowska-Skrzypczak M, Mol A, Poplawski D, Styczynski J, Komarnicki M. Increased risk for invasive aspergillosis in patients with lymphoproliferative diseases after autologous hematopoietic SCT. Bone Marrow Transplant. 2009;43(2):121-6.
12. Andhavarapu S, Roy V. Immunomodulatory drugs in multiple myeloma. Expert Rev Hematol. 2013;6(1):69-82.