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Low rates of invasive fungal disease in patients with multiple myeloma managed with new generation therapies: Results from a multi-centre cohort study

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Abstract

Introduction

A multi-centre study to determine the outcomes and risks for invasive fungal disease (IFD) in myeloma (MM) patients treated with second generation immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies was conducted.

Methods

Clinical and microbiology records were reviewed to capture patient demographics, disease characteristics, treatment, IFI episodes and outcomes. Categorical and continuous variables between patients with IFD and without IFD were compared using Chi-square test, Fisher exact test and Mann-Whitney rank sum test respectively with p value <0.05 considered statistically significant.

Results

Five out of 148 (3.4%) MM patients were diagnosed with five episodes of IFI: 3 were proven, 1 probable, and 1 possible. Median time from commencement of new generation therapy to IFD diagnosis was 4.0 months (Interquartile range [IQR]: 3.4-5.7). In patients with IFD, median cumulative steroid dose over 60 days was 1119 mg (IQR: 1066 – 1333mg). None of the patients with IFD had prolonged neutropenia (neutrophil count <0.5 x 10^9/L for more than 10 days). Common sites of infection were the respiratory tract (40.0%) and bloodstream (40.0%). *Cryptococcus neoformans*

(n=2) and *Candida krusei* (n=1) were the fungal pathogens isolated in the three proven cases. 30-day mortality rate was 40.0%. Patients with IFD were younger (median 58 versus 68 years, $p = 0.52$) and treated with more lines of therapy (median 5 versus 3, $p = 0.04$).

Conclusion

IFD rate is low in heavily treated MM patients treated with second-generation therapy including monoclonal antibodies. Patients do not appear to have traditional risk factors such as prolonged neutropenia.

Introduction

Novel treatments for multiple myeloma (MM) continue to advance with second-generation immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs) such as pomalidomide, carfilzomib, and daratumumab [1]. Previous studies have reported low rates of invasive fungal disease (IFD) in MM patients treated with early generation IMiDs and PI [2-4]. However, higher IFD rates of up to 15% were noted in patients who have been heavily pre-treated[2]. New generations of IMiDs, PIs and immune therapies are increasingly used for relapsed and refractory disease but their impact on IFD risk remains undefined. This study was conducted to determine the burden, outcomes and risks for IFD in MM patients treated with these therapies.

Methods

A multi-centre retrospective cohort study in MM patients treated at Peter MacCallum Cancer Centre and St Vincent's Hospital Melbourne, Australia was conducted. Patients with MM treated with new generation treatments from January 2013 to December 2018 were identified from pharmacy and clinical records for inclusion. For this study, pomalidomide, carfilzomib, isatuximab, daratumumab and elotuzumab were considered to be new generation treatments.

Clinical, microbiology and radiology records were reviewed utilising a standardised case report form to capture the following: patient demographics, disease characteristics including MM type and stage, current and previous MM treatment, lines of therapy, use of antifungal prophylaxis, defined risk factors for IFD (neutropenia $<0.5 \times 10^9$/L, corticosteroid use as prednisolone equivalent over 30, 60 days), IFD episodes, its treatment and outcomes (intensive care unit [ICU] admission and 30-day mortality). During this period, standard of care at both centres did not include the routine use of antifungal prophylaxis for patients treated with second generation IMiDs, PI or mAbs. Investigations for suspected IFD were physician directed and generally consisted of high-resolution computer-tomography (CT) scan of chest and sinuses or positron emission tomography (PET) scan followed by direct tissue sampling. Both centres had access to galactomannan and molecular based fungal diagnostics including pan-fungal and Aspergillus specific polymerase chain reaction (PCR) testing.

Lines of therapy were defined according to International Myeloma Workshop criteria [5]. The type of new generation MM treatment received were classified as mAb-based (any regimen containing a mAb +/- other agents), IMiD plus PI (+/- dexamethasone), IMiD-based (IMiD +/- dexamethasone) or PI-based regimens. Cases of IFD were classified as possible, probable, and proven according to 2019 European Organisation for Research and Treatment of Cancer and Mycoses Study Group criteria[6]. In brief, proven infection was defined by the detection of fungus on histology, culture or nucleic acid amplification from sterile site samples (e.g. blood) whilst probable infections were defined by the presence of a host factor, a clinical feature and mycologic evidence. Absence of mycologic evidence defines a possible infection.

Categorical and continuous variables between patients with IFD and without IFD were compared using Chi-square test or Fisher exact test and Mann-Whitney rank sum test respectively with p value <0.05 considered statistically significant. Statistical analysis was performed utilising Stata (Version 13, Statacorp, College Station, Texas, USA). Logistic regression was planned but not performed due to small number of IFD episodes.

The authors confirm that the ethical policies of the journal as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received (Peter MacCallum HREC LNR/50314/PMCC-2019).

Results

Overall, 148 MM patients received new generation therapy at both centres during the study period and were followed up for a median of 13.2 months (interquartile range [IQR]: 6.8-22.9). Five patients (5/148, 3.4%) were diagnosed with five episodes of IFD: 3 were proven, 1 probable, and 1 possible. Among five IFD cases, over half of the patients were male with a median age of 58 years (IQR: 57 – 61) (Table 1). The median time from MM diagnosis to IFD was 10.4 years (IQR: 8.1-11.3) and number of lines of therapy was 5 (IQR: 5 – 7). The IFD rate was 7.0% (3/43), 2.3% (1/44) and 5.0% (1/20) for patients who received mAb-based combination, IMiD and PI and IMiD-based therapy respectively. Median time from commencement of new generation therapy to IFD diagnosis was 4.0 months (IQR: 3.4-5.7). Three IFD episodes occurred with myeloma progression. Four patients had hypogammaglobulinaemia with 2 patients receiving intravenous immunoglobulin replacement. In terms of established risk factors, median cumulative steroid dose over 60 days was 1119 mg (IQR: 1066 – 1333mg) was identified. None of the patients with IFD had prolonged neutropenia, as defined by neutrophil count <0.5 x 10^9/L for more than 10 days. Although none of the patients had prolonged severe lymphopenia (<0.2 x 10^9/L for 10 days or longer) prior to IFD diagnosis, one patient had a lymphocyte count of 0.1 x 10^9/L at the time of infection.

No patients with IFD received prior antifungal prophylaxis. The common sites of infection were the respiratory tract (40.0%) and bloodstream (40.0%). Fever was the common presenting symptom across all IFD episodes. *Cryptococcus neoformans* (n=2) and *Candida krusei* (n=1) were the fungal pathogens isolated in the three proven cases. IFD cases received treatment with voriconazole (n=2), caspofungin (n=1) and liposomal amphotericin and 5-flucytosine (n=2). 30-day mortality rate was 40.0% following IFD diagnosis with deaths not directly attributable to the infection itself. Further details of patient characteristics, clinical presentation and treatment of patients with IFD are summarised in Table 2. There were no significant differences in demographics between patients with or without IFD (Table 1). Patients with IFD compared to those without IFD were younger (median 58 versus 68 years, $p = 0.52$) and significantly, treated with more lines of therapy (median 5 versus 3, $p = 0.04$).

Discussion

New generation IMiD, PI and monoclonal antibodies were first used for the treatment of relapsed or refractory MM but are now increasingly used as initial therapy in combination for the treatment of newly diagnosed MM [7]. These agents improve progression free survival but MM remains incurable and increasing lines of therapy are required to manage progressive disease and maintain disease control [8,9].

New generation therapies such as monoclonal antibodies are more targeted (MM cell surface antigens) and mediate their effects via complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, phagocytosis and direct modulation of antigen function[10]. However, these therapies are often used in combination and their overall impact on the immune system and risk for IFD remains undefined and no recommendations on antifungal prophylaxis exist due to lack of evidence [7].

In this first ever study of IFD in MM patients treated with new generation IMiDs, PIs and MoAbs, the overall rate of IFD is low at 3.4% with five episodes in 5 patients in the absence of routine use of antifungal prophylaxis. The IFD rate was lowest at 2.3% with IMiD and PI therapy and highest at 7.0% with mAb-based combination therapy. Whilst rates below 1.0% have been reported prior to use of IMiD and PIs as standard of care, the rate reported in this study is more in line with rates of 3.8-5.6% seen MM patients treated with first generation IMiDs and PI [3,4,11]. However, patients in this study were heavily pre-treated with a median of 5 lines of therapy, 10.4 years following initial MM diagnosis. This is in contrast to IFD rate of 15% in patients who received 3 or more lines of therapy in an earlier study, which included previous use of conventional chemotherapy [2].

Higher rates of severe neutropenia (CTCAE version 5 Grade 3, 4) have been reported with the addition of monoclonal antibody therapy to IMiD or PI for treatment of relapsed or refractory disease [7]. No patients with IFD in this study had prolonged neutropenia prior to onset of infection. This is in contrast to an earlier study of first generation IMiD or PI, where up to 90% of MM patients with IFD had prolonged neutropenia[2]. Although overall IFD rate was low at 3.4%, patients with IFD have received a significantly higher number of lines of therapy compared to patients without IFD (median of 5 lines vs. 3 lines of therapy). In this study, patients with IFD have had MM for a median of 10 years and most have progressive disease and hypogammaglobulinaemia. Cumulative immune deficits such as progressive lower CD4 and CD19+ cell counts have been observed with increasing lines of conventional chemotherapy for MM and these deficits are associated with increased risk for infection [12]. Increasing disease burden and cumulative high doses of corticosteroids used in most regimens, compounds the immune dysfunction[8]. These factors play a significant role in increasing risk for IFD, beyond the type of MM therapy itself.

IFD occurred at a median of 4.0 months following commencement of new generation IMiD, PI and mAb therapy. Although this is consistent with high frequency of severe infections (grade 3 or above) in the first 4 months of IMiD -based therapies reported in non-transplant eligible patients[13], it is earlier than median of 6.8 months reported for IFD with first generation IMiDs and PI [3].

No cases of *Cryptococcus neoformans* were detected in observational studies of infections including IFD in MM in the era of novel therapies [3,4,14,15]. However, there are increasing case reports of cryptococcal infection in heavily treated MM patients receiving mAb and second generation IMiDs [16]. *Cryptococcus neoformans* accounted for the majority of proven cases of IFD in this study. Whilst next generation therapies are not classically immune suppressive, corticosteroids remain a large component of MM treatment. Patients with IFD had cumulative median corticosteroid dose of 1119 mg over 60 days and corticosteroids remain a significant risk factor for cryptococcal infection in cancer patients [17].

This study has several limitations. The small number of IFD cases limited determination of risk factors (such as corticosteroid use, lines of therapy) independently associated with development of IFD. During the study period, new generation therapies were used in patients with relapsed and refractory MM hence these results are not generalisable to patients with newly diagnosed MM treated with the same therapies. Nonetheless, this is the first study to establish IFD rates with the use of new generation IMiDs, PIs and mAbs.

In conclusion, IFD rate remains low in heavily treated MM patients treated with new generation therapies including monoclonal antibodies. There is insufficient evidence to support the routine use of

antifungal prophylaxis in this patient cohort. In this era patients with IFD do not appear to have traditional risk factors such as prolonged neutropenia but risk from cumulative immune suppression due to increasing lines of therapy require further evaluation.

Author contributions

BWT designed this study with input from all authors. CL and PS performed the research and data analysis. SH, HQ, MS and BWT reviewed the data and its analysis. BWT wrote this manuscript with input from all authors.

Conflict of interest statement

B.W.T. has received grant funding from Merck Sharpe and Dohme (MSD), Sanofi-Pasteur and speaker fees from Gilead Sciences and Janssen-Ciliag. M.A.S. has received untied grants from Gilead Sciences Inc. and MSD and honoraria for presentations from Pfizer, Gilead Sciences and MSD. Other authors have no conflicts to disclose.

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Variable	IFD N=5 (%)	No IFD N=143 (%)	*p*-value
Sex Male Female	 3 (60.0) 2 (40.0)	 89 (62.2) 54 (37.8)	 0.92
Age (median, IQR) years	58 (58 – 64)	68 (61 – 73)	0.12
Previous lines of therapy (median, IQR)	5 (5 – 7)	3 (2 – 4)	0.04
Treatment regimen‡ mAb-based combination¶ IMiD-PI IMiD-based	 3 (60.0) 1 (20.0) 1 (20.0)	 40 (28.1) 43 (30.0) 19 (13.3)	 0.19 0.63 0.67

‡Treatment for myeloma at diagnosis of invasive fungal disease or during study follow-up for patients without fungal disease

¶ mAb-based combinations consist of treatment regimens that contain a monoclonal antibody +/- immunomodulatory drug +/- proteasome inhibitor +/- corticosteroids

IFD: invasive fungal disease; IQR: interquartile range; mAb: monoclonal antibody; IMiD: immunomodulatory drug; PI: proteasome inhibitor

Table 1: Clinical variables of patients with and without invasive fungal disease treated with new generation therapies

Patient	MM treatment	Disease Response	Lines of Therapy	Neutropenia	Cumulative corticosteroid dose (30 days/60 days) mg	Antifungal Prophylaxis	Clinical Presentation	Site of Infection	Microbiology Result	EORTC/ MSG	Treatment	Outcome
59 M	Pomalidomide Isatuximab Dexamethasone	Progressive Disease	7	No	533 / 1066	None	Productive cough, dyspnoea and fever. Radiology: Patchy airspace, ground-glass and interstitial opacity in both lungs	Respiratory Tract	BAL GM positive (0.83)	Probable	Voriconazole	Survived
62 F	Pomalidomide Dexamethasone	Complete Response	5	No	533 / 1066	None	Productive cough, fever, cutaneous lesions	Multiple	CSF: Cryptococcal Antigen positive CSF culture: *Cryptococcus neoformans*	Proven	Liposomal amphotericin + 5-flucytosine followed by high-dose fluconazole	Survived
63 M	Pomalidomide, Carfilzomib, Elotuzumab Dexamethasone	Progressive Disease	8	No	933 / 1600	None	Dry cough, fever, hypoxia, and fatigue. Radiology: Surrounding ground-glass density with irregular consolidation.	Respiratory Tract	Culture and GM negative	Possible	Voriconazole	Death
56 F	Carfilzomib, Thalidomide Dexamethasone	Partial Response	2	No	533 / 1333	None	Fever, rigor, lethargy	Bloodstream	Blood culture positive for *Cryptococcus neoformans*	Proven	Liposomal amphotericin + 5-Flucytosine	Survived

69 M	Daratumumab Melphalan	Progressive disease	5	No	586 / 1119	None	Fever, hypotension, loss of visual acuity	Bloodstream	Blood culture positive for *Candida krusei*	Proven	Caspofungin	Death

MM: multiple myeloma; EORTC: European Organisation for Research and Treatment of Cancer; MSG: Mycoses Study Group; BAL: broncho-alveolar lavage; CSF: cerebral spinal fluid; GM: Galactomannan; M: male; F: Female

Table 2: Clinical features, treatment and outcomes of invasive fungal disease in patients with myeloma