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Epidemiology of bloodstream infections in patients with myeloma receiving current era therapy

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Abstract

Background

Bloodstream infections (BSIs) are a significant complication of treatment for multiple myeloma (MM). The objective of this study was to define the epidemiology of BSI with current era MM treatment regimens, including immunomodulatory drugs, proteasome inhibitors and autologous haematopoeitic stem cell transplantation (ASCT).

Methods

Clinical and microbiology records of patients with MM diagnosed between 2008 and 2012 were reviewed using a standardised tool to capture patient demographics, myeloma characteristics, and BSI characteristics (type, severity, outcomes). Conditional risk set modeling for multivariate survival data was used to determine clinical predictors of BSI.

Results

Of 199 studied patients, 71 (35.6%) had confirmed BSI (98 infection episodes). Peak incidence was 65.1 infections/100 patient-years at 3-6 months following MM diagnosis with a late peak at 63-66 months. Gram-positive pathogens were responsible for the majority (54.5%) of infections during induction while gram-negative pathogens were responsible for the majority (57.7%) of infections during disease progression. Overall, *E. coli* was the most frequently identified pathogen. *S. pneumoniae* comprised 6.1% of all BSIs at a median of 7.5 months following MM diagnosis. Highest rates of ICU admission (23.1%) and mortality (11.5%) were seen with BSIs in patients with progressive disease. Recent ASCT was independently associated with increased BSI risk (HR 3.09, p=0.05).

Conclusions

Treatment of progressive disease is a high-risk period for infection, evidenced by high proportions of BSI due to gram-negative pathogens and *S. pneumoniae*. Targeted evaluation of preventative strategies (prophylaxis, vaccination) to reduce morbidity and mortality during this period is required.

Keywords: bloodstream infection; myeloma; epidemiology; risk

Introduction

Infections are a leading cause of morbidity and mortality in patients with multiple myeloma (MM) with approximately 50% of early deaths in MM due to infection (1). Disease-related immune deficits have been associated with severe pneumonia and bloodstream infections (BSIs) with encapsulated bacteria such as *Streptococcus pneumonia*. Historically, these infections were most prevalent in untreated patients or early during induction therapy (2, 3).

With evolution of treatments for MM, including use of conventional chemotherapy and autologous haematopoietic stem cell transplantation (ASCT), there has been a change in the aetiology of BSIs, with increasing incidence of infections due to gram-negative bacilli (GNB) (1). More recently, the treatment paradigm for MM has shifted to immunomodulatory drugs (IMiDs), proteasome inhibitors (PI) and consolidation with ASCT in eligible patients. The impact of these changes on the nature and risk of BSIs is undefined.

The objective of this study was to define the epidemiology, risk periods and clinical predictors of BSI with the use of current standard of care treatments for MM to enable targeting of preventative measures.

Methods

Study population

For this study, a subgroup evaluation of a larger cohort study was performed. Details of study design, inclusion criteria and overall study population have been described(4). In brief, patients with MM diagnosed between January 2008 and

December 2012 who received management at the Peter MacCallum Cancer Centre (PMCC) were identified and followed until the completion of management at PMCC, death or until 31 July 2014. Clinical and microbiology records of eligible patients were reviewed using a standardised tool to capture patient demographics, myeloma characteristics (type, stage, therapy), and BSI characteristics (type, severity, outcomes) and risk factors (indwelling venous access device, recent neutropenia below 1.0×10^9/L). Routine antibacterial prophylaxis was not administered at PMCC for any MM treatment during the studied period. Trimethoprim-sulfamethoxazole was routinely administered for *Pneumocystis jirovecii* prophylaxis during ASCT (from neutrophil recovery up to 3 months post-ASCT).

Definitions

MM treatment periods were defined as:

- *Induction* - the period from initial diagnosis to receipt of 4–6 cycles of induction chemotherapy;
- *ASCT* - the period from receipt of chemotherapy for stem cell mobilisation to day 30 following stem cell re-infusion;
- *Plateau* - the period with stable paraprotein levels with (or without) maintenance treatment; and
- *Progression* - any period of increasing myeloma burden despite active anti-myeloma treatment necessitating a change of therapy.

The significance of BSIs was determined in accordance with accepted Centers for Disease Control/National Healthcare Safety Network criteria (5). Isolation of a recognised pathogen (e.g. *S. aureus*) from 1 or more blood cultures was considered significant. For common commensal bacteria (e.g. coagulase-negative staphylococci) to be regarded as significant, the organism must have been identified in two or more blood cultures drawn on separate occasions in the presence of symptoms such as fever.

Statistical analysis

Conditional risk set modeling for multi-failure time data was used to determine clinical predictors for BSI. Clinical and treatment factors patient sex, age, Charlson co-morbidity index, myeloma type, stage, type of recent chemotherapy, cumulative corticosteroid use, presence of invasive venous catheter, neutropenia below $1.0X10^9$ and use of trimethoprim-sulfamethoxazole were evaluated. Analyses were performed using Stata (version 13.1, StataCorp Inc., College Station, TX, USA) and $P \leq 0.05$ was deemed statistically significant. The study was approved by the PMCC Human Research Ethics Committee.

Results

A total of 199 patients were studied. Overall, 98 episodes of BSI occurred in 71 patients (35.6%). Patients with BSI had a median age of 63.0 years, 56.3% male and had predominantly ISS stage 1 (47.9%) IgG MM (54.9%). There were no statistically significant difference in characteristics of patients with or without BSI.

The rate of BSI was 16.9 infections per 100 patient-years of follow up, with median time to BSI of 7.0 months from disease diagnosis. BSI rates peaked at 65.1 infections per 100 patient-years at 3 to 6 months following MM diagnosis with a late peak of 41.4 infections at 63 to 66 months (Figure 1). Amongst 37 patients who did not receive ASCT, there were 5 patients with 7 episodes of BSI (13.5%) whilst there were 91 episodes of BSI in 67 of 162 patients who received ASCT (41.4%).

Gram-positive pathogens (GPC) were responsible for the majority of BSI during induction (54.5%) whilst GNB were responsible for the majority of BSI with disease progression (57.7%). In non-ASCT patients, 85.7% of BSI isolates were GNB whilst in ASCT patients, GNB, GPC and mixed pathogens comprised 37.4%, 35.2% and 27.5% of infections, respectively. Amongst single pathogen BSI isolates, *Escherichia coli* was the most frequent pathogen (30.1% of infections). Ten episodes of BSI (10.2%) were caused by a multi-drug resistant pathogen. These included vancomycin-resistant enterococci (*n*=3) and extended-spectrum beta-lactamase producing GNB (*n*=7; 5 *E. coli*, 2 *Klebsiella* spp.).

S. pneumoniae was the causative pathogen in 6 episodes of BSI (6.1% of all episodes, 8.2% of single pathogen isolates), occurring a median of 7.5 months following MM diagnosis. This pathogen was responsible for 18.2% of all BSI episodes during induction, 1.6% during ASCT and 11.5% during disease progression. *S. pneumoniae* was responsible for a larger burden of infections in non-ASCT patients compared with ASCT recipients (14.3% vs. 5.5% of total infections, respectively).

Overall, 11.2% of BSI episodes resulted in intensive care unit (ICU) admission and BSI episodes were associated with a 3.0% 30-day all-cause mortality rate. The highest rates of ICU admission (23.1%) and mortality (11.5%) were seen with in patients with progressive disease. Further details of pathogen type, risk factors and outcomes are summarised in Table 1.

Recent ASCT (within 30 days) was independently associated with increased risk of BSI with hazard ratio (HR) of 3.09 (95% confidence interval [CI] 1.02 – 9.42, p = 0.05). Conversely the use of trimethoprim-sulfamethoxazole was associated with a decreased risk of BSI with HR 0.98 (95% CI 0.96 – 0.99, p = 0.02). No other clinical factor including the use of iMiDs was independently associated with risk of BSI.

Discussion

Historically, encapsulated bacteria such as *S. pneumoniae* were the leading cause of BSI with infections tending to present early – at diagnosis or within the first 2-4 months of induction therapy (6-8). Following increased use of combination conventional chemotherapy, up to 40-60% of infections was caused by gram-negative pathogens (1, 2, 9). There have been no dedicated studies of BSI in patients with MM following the paradigm shift to treatment with iMiDs, PI and ASCT.

This study has defined the epidemiology of BSI in the era of immunomodulatory drug therapy. We detected a slight shift in the peak incidence of BSI to a period 3-6 months following MM diagnosis, at a median duration of 7.0 months with a secondary peak at 63-66 months. These periods of high BSI incidence coincide with stem cell collection and ASCT and treatment for progressive disease, periods during which high doses of conventional chemotherapy are used singly or in combination (1). These regimens are associated with treatment-related toxicities of neutropenia and mucositis, known risk factors for BSI (1, 7, 8). This loss of mucosal integrity may also account for the higher proportion of GNB seen with ASCT and disease progression. Conversely, iMiDs and PI used for induction therapy are not associated with mucositis, which may account for the relatively higher proportion of GPC seen during this period. Recent ASCT was the only clinical factor independently associated with increased risk of BSI with a HR of 3.09. Notably, use of current generation iMiDs and PI was not independently associated with increased infection risk.

In line with early studies, *E. coli* remains a leading pathogen, contributing to 30.1% of BSI (1, 3, 10). In addition, the proportion of BSIs due to GNB is highest at 58% during disease progression. BSIs during this period were also associated with the highest rates of ICU admission (23.1%) and 30-day mortality (11.5%), confirming disease progression as a high-risk period. A reduced risk for infection was also observed in association with use of trimethoprim-sulfamethoxazole (HR 0.98, p = 0.02), suggesting that prospective evaluation of anti-bacterial prophylaxis during the high-risk period of disease progression should be considered.

Our data demonstrate that *S. pneumoniae* infections are infrequent (6.1% of all BSI episodes) with the use of current therapies, when compared to earlier studies (2). Timing of onset for these infections was also found to be later (median 7.5 months following MM diagnosis), compared to onset during the first 2 months in earlier studies (2, 6). However, this pathogen was still responsible for 18.2% and 11.5% of BSIs during induction and disease progression, respectively. Overall, *S. pneumoniae* contributed to 14.3% of all BSI episodes in

non-ASCT patients. Although patients with MM are poor responders to the pneumococcal polysaccharide vaccine, incidence and case-fatality rates for invasive pneumococcal disease (IPD) remain respectively 15-fold and 2-fold higher in immunocompromised patients (11). Currently available pneumococcal conjugate vaccines (PCV13) are more immunogenic with longer duration of antibody response (3, 12, 13). In non-ASCT patients, we identified induction therapy and progressive disease treatment periods to be higher risk for pneumococcal BSI and targeted use of PCV13 to prevent IPD should be considered in these contexts.

Our study has several limitations. The retrospective nature of this study limited the ability to uniformly obtain data regarding the presence of mucositis and previous pneumococcal vaccination. Dedicated surveillance of indwelling central venous access devices was not performed across our centre, limiting detailed analysis of central line-associated BSI rates. Furthermore, the studied cohort may not be representative of patient populations in other centres, with a high proportion of patients managed with ASCT. However, we did evaluate and report patterns of infection in non-ASCT patients.

Our study of BSI in patients with MM identified treatment of progressive disease as a key high-risk period affected by high proportions of GNB and *S. pneumonia,* associated with high morbidity and mortality. Targeted studies evaluating trimethoprim-sulfamethoxazole prophylaxis duration and other preventative strategies (such as PCV13 vaccination) are required.

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Conflict of interest

SJ Harrison has received research funding and honoraria from Celgene, Novartis, Amgen, Takeda, Sanofi and Janssen Cilag and research funding from Abbvie. MA Slavin has received research funding and honoraria from Pfizer, Merck Sharpe and Dohme and research funding from Gilead.

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	Induction (% total BSI)	**ASCT** (% total BSI)	**Progression** (% total BSI)
Total BSI	11	61	26
Pathogen category			
Gram-positive	6 (54.5)	21 (34.4)	6 (23.1)
Gram-negative	3 (27.3)	22 (36.0)	15 (57.7)
Polymicrobial	2 (18.2)	18 (29.5)	5 (19.2)
Aetiology	*Streptococcus* spp. [n=3][a] CNS [n=2] *Clostridium* spp. [n=1] *Escherichia coli* [n=3]	*Streptococcus* spp. [n=7][b] MSSA [n=4] CNS [n=8] VRE [n=1] *Corynebacterium* spp. [n=1] *E. coli* [n=11] *Pseudomonas* spp. [n=5] *Klebsiella* spp. [n=3] *Citrobacter* spp. [n=2] Gram-negative not specified [n=1]	*Streptococcus* spp. [n=4][c] VRE [n=1] *Norcadia* spp. [n=2] *E. coli* [n=8] *Klebsiella* spp. [n=4] *Salmonella* spp. [n=1] Gram-negative not specified [n=2]
Risk factors			
Indwelling venous access device			
PICC	3 (27.3)	50 (82.0)	13 (50.0)
CVC	1 (9.1)	1 (1.6)	0 (0.0)
implanted port	0 (0.0)	5 (8.2)	0 (0.0)
Permacath	0 (0.0)	2 (3.3)	2 (7.7)

Neutropenia (<1.0 × 10^9/L)	6 (54.5)	58 (95.1)	17 (65.3)
Trimethoprim-sulfamethoxazole	7 (63.6)	56 (91.8)	20 (76.9)
Outcomes			
ICU admission	1 (9.0)	4 (6.6)	6 (23.1)
Death	0 (0.0)	0 (0.0)	3 (11.5)

ASCT: autologous haematopoeitic stem cell transplant; CNS: coagulase negative Staphylococcus; VRE: vancomycin resistant enterococcus; PICC: Peripherally inserted central catheter; CVC: Central venous catheter; ICU: intensive care unit

[a] *Streptococcus pneumoniae* in 2 instances, [b] *S. pneumoniae* in 1 instance, [c] *S. pneumoniae* in 3 instances

Table 1: Aetiology, risks and outcomes of bloodstream infections according to myeloma treatment period

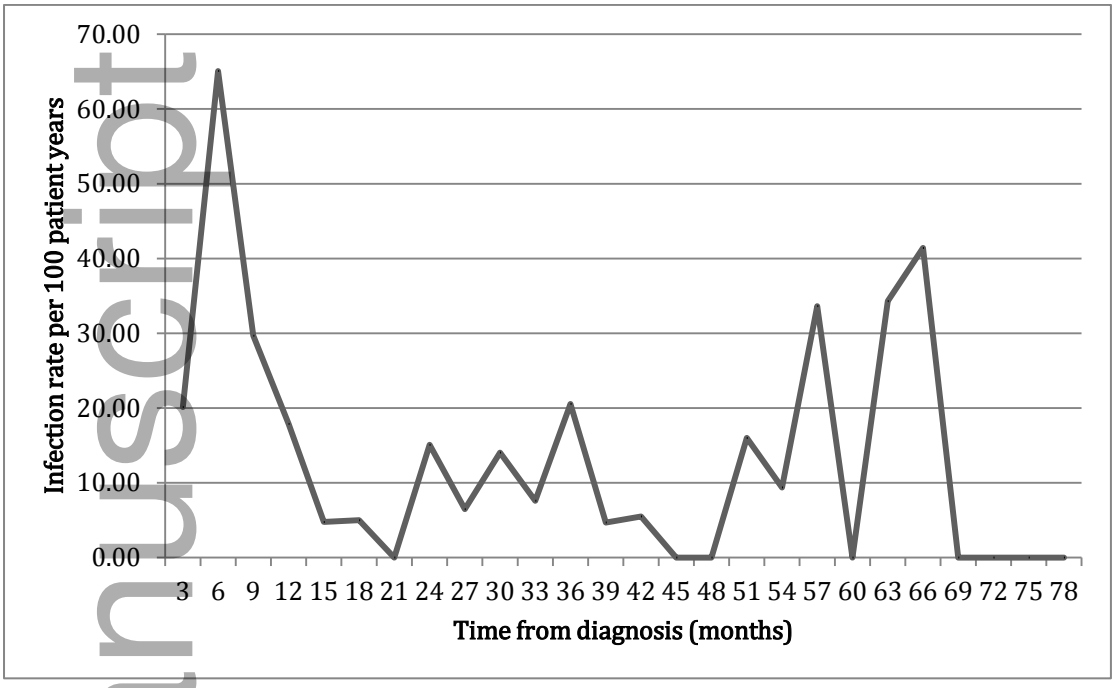

Figure 1: Quarterly rates of blood stream infection in patients with myeloma following disease diagnosis