Infection Burden and Survival Outcomes in Multiple Myeloma Patients with Acquired Hypogammaglobulinemia Receiving Antibiotic Prophylaxis without IVIG: A Single-Center Real-World Study

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ABSTRACT

Infections remain one of the leading causes of morbidity and mortality in patients with multiple myeloma (MM), particularly during the first three months following diagnosis. This study specifically aimed to evaluate the infection burden and survival outcomes in MM patients with acquired hypogammaglobulinemia receiving antibiotic prophylaxis alone. This retrospective single-center study included 22 MM patients diagnosed with acquired hypogammaglobulinemia between January 2020 and December 2022. Hypogammaglobulinemia was defined as IgG < 500 mg/dL (excluding paraproteins). Patients received levofloxacin prophylaxis for the first 3 months after diagnosis, followed by trimethoprim/sulfamethoxazole and valacyclovir throughout the treatment process. The median age was 66.9 years (range: 53-88), and 63.6% of patients were ≥65 years old and 59.1% of the patients were male. A total of 43 infections were recorded, with pneumonia being the most common (30.2%). Only 4 patients (18.2%) required hospitalization due to infection, and 2 patients (9.1%) had neutropenia during the infection period. The median overall survival (OS) was 22 months (range: 1-85), with 7 deaths (31.8%) recorded, and only 1 (4.5%) was infection-related. Patients with light chain myeloma had a higher incidence of infections compared to other myeloma types (p= 0.02). Hospitalization due to infection was associated with shorter OS (p= 0.002). Our findings suggest that antibiotic prophylaxis may help limit severe infections and infection-related mortality in MM patients with hypogammaglobulinemia, particularly in the early phase of treatment. Further studies are warranted to determine optimal prophylactic strategies in this high-risk subgroup.

Keywords: Multiple Myeloma, Hypogammaglobulinemia, Antibiotic Prophylaxis, Levofloxacin, IVIG Replacement

INTRODUCTION

Multiple myeloma (MM), the third most common hematologic malignancy after lymphoma and leukemia, accounted for 0.9% of all cancers and 1.1% of cancer deaths worldwide in 2018.[1] In patients with MM, whose prevalence is increasing with advancing age, patient-related factors such as age, comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, human immunodeficiency virus (HIV), etc.), smoking habits, as well as disease- and treatment-related infections are among the most important causes of morbidity and mortality.[2-4] Research conducted during periods of intensive chemotherapy use and subsequent to the 2000s has demonstrated that the mortality rate within the initial 60-90 days ranges from approximately 10-22%, with 22-50% of fatalities attributed to infection.[5-7] Compared to population-based age-matched controls, respiratory tract infections, pneumonia, septicemia and urinary tract infections are more common in MM patients, with a 7.7, 15.6 and 16.6 times higher risk of developing pneumonia, septicemia or meningitis, respectively.[6]

This increased risk of infection, which is an important problem in MM patients, is due to immunodeficiency caused by age, comorbidities, and dysfunctions in both cellular (e.g., T-cell, dendritic, natural killer cell) and humoral (notably B-cell and hypogammaglobulinemia) immunity, as well as neutropenia and treatment agents.[5,7-15]

In particular, the approach of the use of prophylactic antibiotics/antiviral agents and intravenous immunoglobulin (IVIG), which are generally accepted as the two most important strategies to prevent infection in MM patients, alongside vaccination as an additional option, remains unclear.[16] Their relative effects are difficult to assess due to considerable variation in patient characteristics, disease course, and treatment practices.[17]

Most data supporting IVIG prophylaxis come from the chemoimmunotherapy era, showing reductions in infection, antibiotic use, and hospitalization, but not in mortality.[17,18] While antibiotic prophylaxis has proven effective in neutropenic leukemia patients,[19] neutropenia-related infections are rare in newly diagnosed MM, where early infections are mostly due to immune dysfunction.[5,8] Evidence on antibiotic prophylaxis in MM—particularly in those with hypogammaglobulinemia—is limited, though some studies suggest trimethoprim/sulfamethoxazole may reduce infections.[20,21] A meta-analysis found no survival benefit despite reduced infections,[22] while a recent large randomized controlled trial demonstrated that levofloxacin reduced both infections and mortality.[8] In hypogammaglobulinemic patients, data remain scarce, and a study comparing IVIG and antibiotic prophylaxis in hematologic malignancies found no difference in major infections or survival.[23] Overall, the optimal strategy for antibiotic prophylaxis in MM patients with hypogammaglobulinemia remains to be defined.

With the significant changes in the treatment paradigm of multiple myeloma over the years, a reevaluation of infection prophylaxis strategies has become inevitable. In this study, we aimed to specifically assess the infection burden and survival outcomes in patients with multiple myeloma (MM) who developed acquired hypogammaglobulinemia and were managed with antibiotic prophylaxis alone. By focusing on this unique patient subgroup, we aim to provide real-world data regarding the clinical impact of antibiotic prophylaxis in the current treatment era.

PATIENTS AND METHODS

Patients with acquired hypogammaglobulinemia diagnosed between January 2020 and December 2022 in the Hematology Department of Health Sciences University Antalya Training and Research Hospital between January 2020 and December 2022, who had acquired hypogammaglobulinemia at the time of diagnosis or at a different treatment step and who were followed up with antibiotic prophylaxis were included in the study. Patients who were followed up with IVIG prophylaxis, whose follow-up period was shorter than 12 months, who had additional immunodeficiency status due to hereditary or other acquired causes such as HIV, and whose data could not be accessed were excluded from the study. Data were collected from patient files, electronic hospital database and hospital central laboratory records.

Absolute immunoglobulin G (IgG) level < 500 mg/dL (excluding paraprotein) was considered hypogammaglobulinemia.[24,25] In patients with IgG-type multiple myeloma, hypogammaglobulinemia was assessed by estimating the polyclonal IgG concentration. This was calculated by subtracting the monoclonal IgG component (M-protein) from the total serum IgG value using the following formula: Polyclonal IgG= Total IgG – M-protein. M-protein concentration was determined by serum protein electrophoresis (SPEP), and quantified using densitometric analysis of the gamma region. This approach reflects the routine laboratory practice in our institution for assessing immunoparesis in IgG-type myeloma and has also been described in the literature.[25]

Antibiotic prophylaxis was defined as levofloxacin (500 mg/day) in the first 3 months after diagnosis, trimethoprim/sulfamethoxazole (160/800 mg[3] days/week) after 3 months (120 days) regardless of IgG level, and valacyclovir (500 mg/day) during the entire treatment period after diagnosis. The diagnosis of infection was based on clinical and laboratory findings at outpatient and emergency

visits, as well as positive radiologic findings and positive microbiologic cultures indicative of infection according to standard practice.[26] Severity grading of infections could not be applied due to the retrospective nature of the study; however, hospitalization status, related causes, and infection-related mortality were identified based on clinical documentation.

Statistical Analysis

IBM SPSS Statistics (version-23) was used for the statistical analysis. Descriptive statistics were used to present the data. Categorical data are presented as numbers and ratios, and numerical data are presented as medians, minima, and maxima. Significant differences between the data were analyzed using the Chi-Square tests for independent variables. Kaplan-Meier survival analysis was applied for OS, and log-rank tests were used to examine the factors affecting survival. Statistical significance was defined as a p-value ≤ 0.05.

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of S.B.U. Antalya Training and Research Hospital (Date: August 08, 2024, Decision No: 11/18).

RESULTS

Patients and Infection Situations

22 patients with MM with acquired hypogammaglobulinemia, 13 (59.1%) of whom were male, were included in the study. The mean age was 66.9 years (53-88) and 14 (63.6%) patients were aged ≥ 65 years. A total of 9 (40.9%) patients (6 kappa, 3 lambda) had light chain, 8 (36.4%) IgA and 5 (22.7%) IgG type M-protein disease. Thirteen (59.1%) patients had International Staging System (ISS)-3 disease. A total of 27 treatment episodes of acquired hypogammaglobulinemia were identified, 19 in first-line treatment and 3 in other treatment lines and 5 in multiple lines. The most commonly used regimens during these periods were VCD (bortezomib, cyclophosphamide, and dexamethasone), used in 9 patients (33.3%), and VRD (bortezomib, lenalidomide, and dexamethasone), used in 10 patients (37%), almost all in first-line settings.

Table 1. Demographic, clinical and treatment data of the patients

Characteristics		Number (n= 22) (%)
Age (Median)		66,9 (53-88)
≥ 65		14 (63.6)
< 65		8 (36.4)
Sex		
Female		9 (40.9)
Male		13 (59.1)
Comorbidity		
Hypertension		5 (22.7)
Diabetes mellitus		3 (13.6)
Chronic kidney disease		3 (13.6)
Coronary artery disease		2 (9.1)
Chronic obstructive pulmonary disease		1 (4.5)
M-Protein type		
Light chain (kappa/lambda)		9 (6/3) (40.9)
IgA_(kappa/lambda)		8 (5/3) (36.4)
IgG_(kappa/lambda)		5 (2/3) (22.7)
ISS staging		
ISS-1		5 (22.7)
ISS-2		4 (18.2)
ISS-3		13 (59.1)
Hypogammaglobulinemic lines		
Total		27 (100%)
1. line		19 (70.4)
≥ 2. line		3 (11.1)
Multiple lines		5 (18.5)
Laboratory during hypogammaglobulinemia		
IgG, mg/dL, mean (range)		353.7 (170-498)
Neutrophile /mm^3, mean (range)		3850 (400-11600)
Lymphocyte /mm^3, mean (range)		1649 (120-3260)
Treatments during periods of hypogammaglobulinemia	**Only 1. line (n=19) (%)**	**All (n= 27) (%)**
VCD	9 (47.4)	9 (33.3)
VRD	9 (47.4)	10 (37.0)
RD	1 (5.2)	2 (7.4)
DVd		2 (7.4)
KRD		2 (7.4)
PVD		2 (7.4)
Number of patients who underwent ASCT		5 (22.7)

Ig: Immunoglobulin, ISS: International staging system. Treatments; ASCT: Autologous stem cell transplant, DVd: Daratumumab, bortezomib and dexamethasone, KRD: Carfilzomib, lenalidomide and dexamethasone, PVD: Pomalidomide, bortezomib and dexamethasone, RD: Lenalidomide and dexamethasone, VCD: Bortezomib, cyclophosphamide and dexamethasone, VRD: Bortezomib, lenalidomide and dexamethasone.

In addition, only 5 patients received autologous stem cell transplantation (ASCT). Demographic, clinical and treatment characteristics of the patients are given in Table 1.

A total of 43 infections were recorded clinically and/or microbiologically. Among 22 patients, 5 (22.7%) had no infection, 7 (31.8%) had ≤ 1 infection and 12 (54.5%) had ≤ 2 infections. Pneumonia was the most common infection in 9 (40.9%) of the patients with a total of 13 (30.2%) infections, followed by upper respiratory tract infections with 7 (16.2%) infections. A total of 4 (18.2%) patients required hospitalization, 2 for pneumonia, 1 for acute appendicitis and 1 for catheter infection. Only 2 (9.1%) had neutropenia (< 1000/mm^3) during the infection period and these patients did not require hospitalization. A total of 5 patients (22.7%), including 3 patients with pneumonia (one caused by SARS-CoV-2), one with catheter infection and one with acute appendicitis, received a single dose of IVIG (400 mg/kg) in addition to antibiotherapy only at that time on physician initiative. Detailed information about the infections of the patients during the period accompanied by hypogammaglobulinemia is given in Table 2.

The relationship between demographic, clinical and laboratory characteristics of the patients and the development of infection (no infection vs. at least one infection; ≤ 2 infections vs. > 2 infections in 54.5% of the patients (12 patients); pneumonia vs. no pneumonia; and infection requiring hospitalization vs. no infection) was analyzed (Table 3). There was no difference between those aged ≥ 65 years and those aged ≥ 65 years (p= 0.36), between men and women (p= 0.60), and between those with an ISS of 3 and those without (p= 0.60) in terms of never or at least once developing an infection. All three conditions (age, gender and ISS) did not affect whether the number of infections was >2 (p= 0.66, p= 0.41, p= 0.41, respectively). Among light chain myeloma patients, none of the 5 patients with a history of at least one infection and none of the 5 patients with no infections had light chain myeloma. The number of patients with both > 1 and >2 infections was higher among light chain myeloma patients than among patients without light chain myeloma (p= 0.05, p= 0.02, respectively). There was no difference between patients who received VCD therapy and those who received VRD and between patients who underwent ASCT and those who did not, both in terms of having no infections (p= 1.0 and p= 0.29, respectively) and having ≤ 2 infections (p= 0.37 and p= 1.0, respectively). However, all 5 patients with ASCT had at least one recorded infection. Age (≥ 65 vs. < 65), gender, ISS (3 vs. 1-2), light chain myeloma, receiving VCD or VRD treatment, and ASCT status had no effect on the history of pneumonia and infections requiring hospitalization.

Table 2. Infectious data of the patients.

Characteristics		Number (n= 22) (%)
Patients with clinically and/or microbiologically documented infections		
0 infections		5 (22.7)
1 infection		2 (9.1)
2 infections		5 (22.7)
3 infections		6 (27.2)
≥ 4 infections		4 (18.2)
Distribution of clinically and/or microbiologically documented infections		
Total documented infection count	43 (%)	17 (77.3)
Pneumonia	13 (30.2)	9 (40.9)
Upper respiratory tract infections	7 (16.2)	5 (22.7)
HSV infections	4 (9.3)	4 (18.2)
SARS-CoV-2 infections	4 (9.3)	4 (18.2)
Urinary tract infections	4 (9.3)	3 (13.6)
Gastroenteritis	3 (6.9)	2 (9.1)
Candidiasis	3 (6.9)	3 (13.6)
Conjunctivitis	2 (4.6)	2 (9.1)
Acute appendicitis	1 (2.3)	1 (4.5)
Soft tissue infection/cellulitis	1 (2.3)	1 (4.5)
Catheter infection	1 (2.3)	1 (4.5)
Previous HBVserology positivity		4 (18.2)
HBV reactivation		0 (0.0)
Infections requiring hospitalization		4 (18.2)
IVIG replacement due to infection		5 (22.7)
Neutropenia during infection*		2 (9.1)
Infection resulting in death		1 (4.5)

HBV: Hepatitis B virus, HSV: Herpes simplex virus, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

**Neutropenia; < 1500/mm^3*

Table 3. The relationship between patient demographic characteristics and treatments, development of infection, infection requiring hospitalization, and pneumonia

Characteristics		History of infection		
		No	Yes	p
Age	< 65	1	7	0.36
	≥ 65	4	10	
Sex	Female	3	6	0.60
	Male	2	11	
ISS	1-2	3	6	0.60
	3	2	11	
Light chain myeloma	Yes	0	9	0.05
	No	5	8	
Treatment	VCD	2	7	1.0
	VRD	3	7	
ASCT	Yes	0	5	0.29
	No	5	12	
		Number of infections (>2)		
Age	< 65	4	4	0.66
	≥ 65	8	6	
Sex	Female	6	3	0.41
	Male	6	7	
ISS	1-2	6	3	0.41
	3	6	7	
Light chain myeloma	Yes	2	7	0.02
	No	10	3	
Treatment	VCD	4	5	0.37
	VRD	7	3	
ASCT	Yes	3	2	1.0
	No	9	8	
		Infection requiring hospitalization		
Age	< 65	7	1	1.0
	≥ 65	11	3	
Sex	Female	6	3	0.26
	Male	12	1	
ISS	1-2	9	0	0.11
	3	9	4	
Light chain myeloma	Yes	7	2	1.0
	No	11	2	
Treatment	VCD	7	2	1.0
	VRD	8	2	
ASCT	Yes	4	1	1.0
	No	14	3	
		History of pneumonia		
Age	< 65	4	4	0.66
	≥ 65	9	5	
Sex	Female	6	3	0.67
	Male	7	6	
ISS	1-2	6	3	0.67
	3	7	6	
Light chain myeloma	Yes	4	5	0.38
	No	9	4	
Treatment	VCD	4	5	0.37
	VRD	7	3	
ASCT	Yes	1	4	0.11
	No	12	5	

ASCT: Autologous stem cell transplantation, ISS: International staging system , VCD: Bortezomib, cyclophosphamide and dexamethasone, VRD: Bortezomib, lenalidomide and dexamethasone.

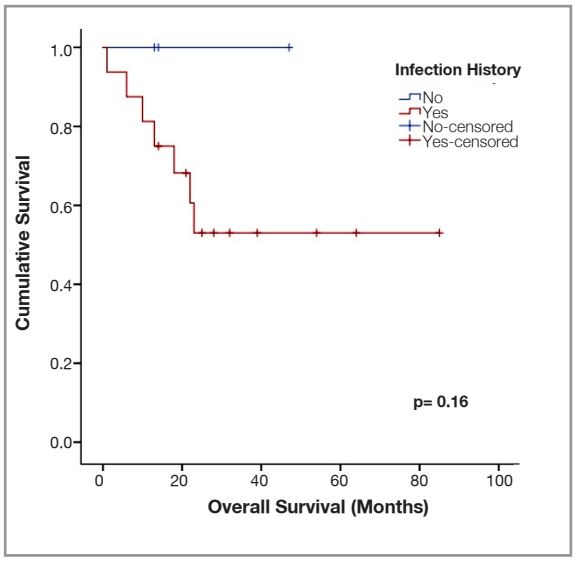

Figure 1. Overall survival of patients stratified by infection history (Yes vs No)

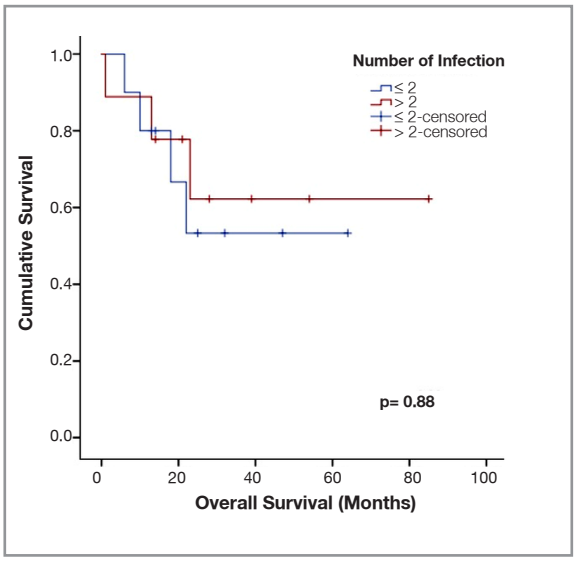

Figure 2. Overall survival of patients stratified by the number of infections (≤ 2 vs > 2).

Overall Survival

The median overall survival (OS) time of the patients was 22 (1-85) months; among the 15 patients still under follow-up, 9 (40.9%) were in remission, while 6 (27.3%) had progressed to relapsed/refractory disease during follow-up. Detailed treatment information for relapsed/refractory patients was not provided, as it was beyond the scope of the study focused on the early infection period; none of these patients received BCMA-directed or bispecific antibody therapies. Only 1 patient (4.5% of all patients, 14.2% of patients who died) died due to infection (catheter-related) during the period of hypogammaglobulinemia, and 7 (31.8%) patients died in total. Median OS was not reached in patients under 65 years, while it was 22 months in those aged ≥ 65 years (p= 0.21). Male patients had longer median OS than females (not reached vs. 13 months, p=0.08), which may be related to age distribution (53.8% of men vs. 77.7% of women were aged ≥ 65). No significant OS differences were observed between light chain and other myeloma types (p= 0.54), or between ISS-3 and non–ISS-3 patients (p= 0.84). Median OS was longer in patients who received ASCT (not reached) compared to those who did not (14 months, p=0.05). A non-significant OS advantage was also observed in patients treated with VRD (not reached) versus VCD (23 months, p= 0.21).

The effect of patients' infection status on OS was evaluated. Patients with at least one infection had a shorter OS compared to patients with no infection, but not significantly (p= 0.16) (Figure 1). The OS times of the 12 patients with 2 or less infections (54.5%) and those with more than 2 infections were similar (p= 0.88) (Figure 2). However, patients with a history of infection requiring hospitalization had a shorter median OS (10 months) than the others (not reached) (p= 0.002) (Figure 3). OS times were similar in patients with and without pneumonia, the most common infection (p= 0.95) (Figure 4).

DISCUSSION

In this study, we present real-world data on infection outcomes in MM patients with acquired hypogammaglobulinemia who were managed exclusively with antibiotic prophylaxis. Among 22 patients, 17 (77.2%) experienced at least one infection, yet only 4 patients (18.2%) required hospitalization. Respiratory tract infections were the most commonly documented type, accounting for 20 of the 43 infection episodes (46.4%). Notably, we also observed an association between light chain multiple myeloma and increased infection frequency. Although the underlying mechanism remains unclear, this may reflect deeper immuno-

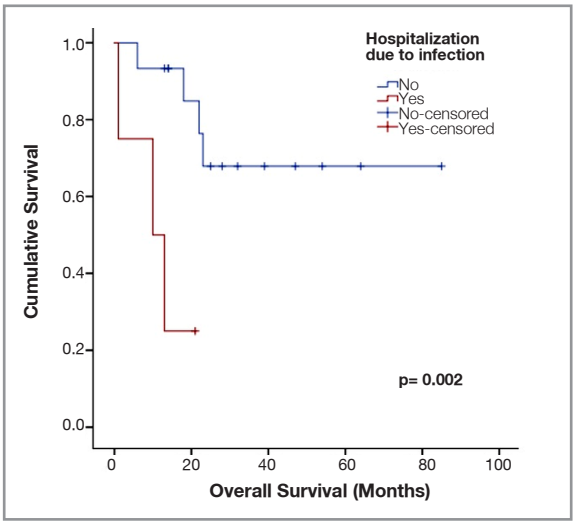

Figure 3. Overall survival of patients stratified by hospitalization due to infection (Yes vs. No).

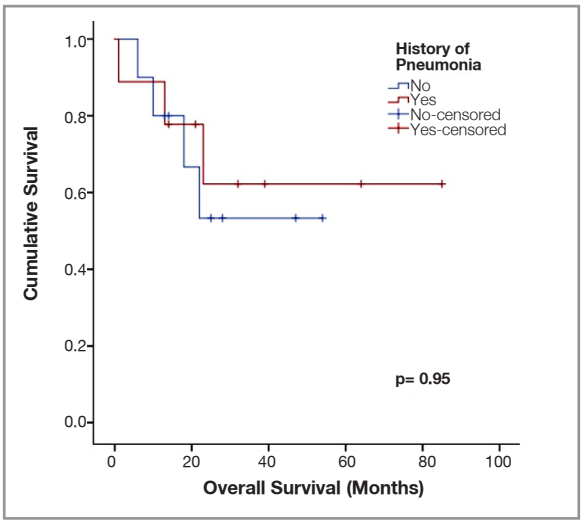

Figure 4. Overall survival of patients stratified by history of pneumonia (Yes vs. No).

suppression or more aggressive disease biology in this subgroup. Finally, infection-related mortality occurred in only one patient (4.5%), highlighting a potentially protective role of early antibiotic prophylaxis in this high-risk population.

In all MM patients, the incidence of infection within the first 60-90 days has been reported to be 18–23% in those receiving antibiotic prophylaxis, with respiratory tract infections (upper and lower) accounting for approximately 40% of cases. Grade 3-4 infections requiring hospitalization occur in about 8%, and mortality is reported at around 1-1.5%.[20,21] In contrast, a retrospective study of 45 MM patients with hypogammaglobulinemia, 14 of whom received antibiotic, antiviral, and antifungal prophylaxis and 3 received IVIG, found that 91% experienced at least one infection and 48.8% had two or more infections within the first year. Respiratory infections were the most common (37.8%), and one-year mortality was 33%.[24] In this study, which included only MM patients with hypogammaglobulinemia receiving antibiotic prophylaxis, the infection rate and distribution were similar to those reported in the above cohort. However, our hospitalization rate aligned more closely with that of the general MM population, and the infection-related mortality was lower than in the hypogammaglobulinemic cohort, while comparable to the overall MM population. These findings may suggest that carefully administered antibiotic prophylaxis in the early high-risk phase could help prevent serious infections and related mortality, even if it does not reduce the total infection burden.

The introduction of proteasome inhibitors (PIs), immunomodulatory drugs (IMIDs), and monoclonal antibodies has significantly improved response rates, OS, and progression-free survival in MM patients.[27,28] However, infections—especially in the first 3 months—remain a major cause of morbidity and mortality, primarily due to immunodeficiency from age, comorbidities, disease-related immune dysfunction (hypogammaglobulinemia, T-cell and NK-cell defects), and treatment-induced neutropenia or steroid use.[5-15] Age ≥65 is a known risk factor for infection and mortality,6,7 and 63.6% of our patients were in this group. Comorbidities such as hypertension, diabetes, and chronic kidney disease were rates under 10% at diagnosis and lower in patients treated with IMIDs/PIs versus traditional chemotherapy[5,8], though CD38 antibodies like daratumumab have increased neutropenia and infection risks.[12-14] In our study, neutropenia occurred in only 2 patients (9.1%) during infection. HSV infection was observed in 4 patients (18.2%), while no VZV cases were detected, despite the known association with bortezomib use.[9]

In addition to disease- and treatment-related immune dysfunction, hypogammaglobulinemia itself represents an independent and significant risk factor for infections in MM patients.[15] This risk is

highest within the first year—and particularly the first 3 months—of diagnosis, and IgG levels below 500 mg/dL are considered a poor prognostic factor in MM.[24,29] Unlike CLL and NHL, where chemoimmunotherapy remains standard, MM patients are increasingly treated with targeted agents, raising expectations that immunoparesis and hypogammaglobulinemia may improve with disease control. However, optimal prophylactic strategies for patients with persistent hypogammaglobulinemia remain unclear.

Traditional preventive approaches in MM include antibiotics, antivirals, IVIG replacement, and vaccination. However, vaccination, particularly in hypogammaglobulinemic patients, often results in suboptimal antibody responses due to underlying immune dysfunction. Although studies on vaccine efficacy are limited and show mixed results, VZV and influenza vaccines have been associated with reduced infection rates, but not with improved survival.[16,17] Unlike vaccination, IVIG and antibiotic prophylaxis, which may be protective against more agents, have been used in these patients for years.

Most studies evaluating IVIG prophylaxis were conducted before the 2000s, during the chemotherapy era, and showed reductions in major infections, antibiotic use, and hospitalizations, without a survival benefit.[17,18] Antibiotic prophylaxis has been widely accepted in afebrile neutropenic patients with hematologic malignancies, mostly leukemias, based on early data showing reductions in infection incidence and mortality.[19] However, evidence remains limited in immunosuppressed patients without neutropenia, such as those with MM. Over time, changes in treatment algorithms and pathogen profiles have influenced prophylaxis strategies in MM.[30] For example, antifungal prophylaxis, once common during intensive chemotherapy and allogeneic transplant periods, has largely been discontinued with the adoption of IMIDs, PIs, and ASCT as standard treatments.[31,32] Consistent with this, no antifungal prophylaxis was used in our cohort.

The increased risk of VZV reactivation associated with CD38-targeted therapies and bortezomib has been shown to decline with acyclovir or valacyclovir prophylaxis, which is recommended even after VZV vaccination.[9,33] In our study, valacyclovir prophylaxis was routinely used from diagnosis through treatment. While an early prospective trial showed that trimethoprim/sulfamethoxazole (TMP-SMX) reduced serious infections[20], another study did not confirm similar benefits for TMP-SMX or ciprofloxacin.[21] A recent meta-analysis found that antibiotic prophylaxis during the first 3 months of MM treatment reduced infection rates but did not impact all-cause mortality, even though hypogammaglobulinemia is more common than prolonged neutropenia in this period.[22]

Despite advances in MM therapies leading to improved outcomes, there remains limited evidence regarding the optimal prophylactic approach for newly diagnosed MM patients with hypogammaglobulinemia, particularly during the high-risk first 3 months. In a randomized trial of 977 newly diagnosed MM patients, levofloxacin prophylaxis (500 mg/day) reduced febrile infections and mortality compared to control, although hypogammaglobulinemia was not specifically assessed.[8] A recent randomized study comparing IVIG given every four weeks and daily trimethoprim/sulfamethoxazole in patients with hematologic malignancies and hypogammaglobulinemia, including only 12 multiple myeloma patients, showed no significant difference in major infections or OS between the two groups.[23] These findings highlight the need for further studies focusing on MM patients with hypogammaglobulinemia during early treatment. The hesitancy in both prophylactic approaches also underscores this need. Concerns about antibiotic prophylaxis include resistance from inappropriate use, while IVIG use remains controversial due to insufficient contemporary evidence, high cost, and the potential for adverse effects, such as acute kidney injury in MM patients.[17,28,34]

This study has several limitations. First, its retrospective design limited access to complete data, particularly regarding patients' vaccination status and genetic risk profiles. Second, the absence of a comparison group—such as patients receiving IVIG prophylaxis or no prophylaxis—restricts the ability to draw definitive conclusions about the specific benefit of antibiotic prophylaxis. Additionally, the small sample size limited the statistical power of our analyses, and the findings should be interpreted as exploratory rather than conclusive.

In conclusion, based on current data, there is still no clear consensus on the optimal infection prophylaxis strategy for hypogammaglobulinemic patients with MM. Current evidence raises important questions regarding the comparative efficacy of levofloxacin versus trimethoprim/sulfamethoxazole, as well as the potential benefit of their combined use over monotherapy or IVIG replacement. Although both agents have shown promise in recent studies, further research is needed in newly diagnosed MM patients to establish evidence-based prophylaxis algorithms, particularly for the early high-risk period.

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