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ORIGINAL ARTICLE

The risk of infections in multiple myeloma before and after the advent of novel agents: a 12-year survey

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Abstract

Infections represent a major cause of morbidity and mortality in multiple myeloma and are linked to both therapy- and disease-related factors. Although it has been suggested that the rate of infections increased since the introduction of novel agents, controversies still exist. To better assess the risk factors associated with infections in the era of novel agents, we conducted a large retrospective analysis of 479 myeloma patients treated at Jena University Hospital over a period of 12 years. During their disease history, 65% of patients developed at least one infection, and 37% of therapies were associated with at least one infectious episode. The rate of infections was constant over the years, with no increase in infectious complications after the routine implementation of novel agents. Infections were mainly bacterial and strongly associated with high disease burden, relapsed disease, and treatment with high-dose chemotherapy. Varicella zoster virus (VZV) reactivations occurred late during treatment (median time between high-dose chemotherapy and VZV reactivation 6 months, range 0–44 months), and fewer patients developed a VZV reactivation after 2009 ($p = 0.001$). Infections are still one of the major causes of morbidity in myeloma patients, and prophylactic measures are urgently needed to reduce this potentially lethal complication.

Keywords Multiple myeloma · Infections · Immunomodulatory drugs · Proteasome inhibitors · Varicella zoster virus · High-dose chemotherapy

Introduction

The advent of novel agents in the treatment of multiple myeloma (MM) has dramatically changed the prognosis of this still incurable disease [1, 2]. Since the introduction of the first in class immunomodulatory drug (IMiD) thalidomide and the first in class proteasome inhibitor (PI) bortezomib, the outcome of MM patients has significantly improved [3–6]. Improvements seem to be even stronger with the second- and third-generation IMiDs and the second-generation PIs.

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Therefore, nowadays, IMiDs or PIs form the backbone of almost all anti-MM treatments [7–12]. Together with an improvement in outcomes, however, the widespread use of new compounds has seen the emergence of a different spectrum of adverse events [13]. Infections are one of the main causes of morbidity and mortality in MM patients, responsible for about 45% of early deaths in this patients' population [14]. The higher rate of infections is not due to an increased occurrence of neutropenia [14], but is rather due to a combination of myeloma-related immunosuppression and treatment-related factors. Compared to the normal population, MM patients have a 7-fold increased risk of developing an infection in the course of their disease. When taking into account only viral infection, this risk increases up to 10-fold [15]. Recent data suggest that, since the introduction of novel agents, the rate of infectious complications has further increased, with a higher risk of infections for patients diagnosed in more recent years [15] and an increase of Varicella zoster virus (VZV) reactivation seen in patients treated with PIs [16]. However, not all studies are concordant, and some groups failed to demonstrate an increased risk of infections for patients receiving IMiDs or PI containing regimens [17].

To shed further light on the complex issue of infections in MM patients and to better assess the risk factors associated with this potentially lethal complication, as well as the role of IMiDs and PIs in its development, we conducted a large retrospective analysis of 479 MM patients treated at Jena University Hospital over a period of 12 years, from 2003 to 2015.

Material and methods

The retrospective study was conducted after approval by the institutional review board at Jena University Hospital in Germany, a tertiary referral center for MM patients. All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008. All consecutive patients with MM referred to our center between 2003 and 2015 were included in the analysis. Patients were identified from electronic medical records. All electronic and paper documentation of the patients was reviewed. Overall, data on 479 patients were retrieved. All patients were followed until death or last day of follow-up whichever occurred first. Patients lost to follow-up were censored on the 30th of April 2014. Data on demographic, baseline hematological and biochemical characteristics, MM parameters (MM subtype, disease stage, disease phase, and treatment received), and comorbidities were extracted from the medical records. Complete data on infectious complications including microbiological confirmation, where available, were recorded. For documentation of bacteremia with coagulase negative staphylococci (CNS), two positive results from subsequent separate sets of blood cultures were required.

To better assess the impact of each single treatment modality on the development of infections, each treatment modality received was defined as a patient case: if a patient received induction treatment, stem-cell mobilization, and two courses of high-dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT), four patient-cases were recorded (one for induction treatment, one for mobilization, and one each for HDM + ASCT). Each patient-case started with the first day of treatment and finished with the first day of administration of subsequent therapy. Lines of therapy were defined according to the International Myeloma Working group recommendation [18].

Standard descriptive statistics were used to summarize the data of patients or (patient-)cases (e.g., continuous: mean ± standard deviation/count: absolute and relative frequencies). Comparisons between two patient groups were performed using Chi-square or Fisher's exact tests for nominal data types or Wilcoxon-Mann-Whitney tests for ordinal or continuous, metric data types. To evaluate potential factors for the infection risk, we applied logistic regression model while using generalized estimating equations to address the clustering within patients. In these models, we report odds ratio estimates with 95% confidence intervals. All reported p values are nominal and two-sided. In this explorative study, we applied a significance level $\alpha = 0.05$ (two-sided). All statistical analyses were done with SPSS (version 24) or the statistical environment R (version 3.5.1).

Results

Rate of infection in the overall population

From the 479 patients analyzed, 1690 patient-cases (from now on called only cases) were reported. Thus, the median number of cases per patient was 3 (range 1–15). Patients' characteristics are summarized in Table 1. Median age of the overall population was 62 years (range 35–89) and about 80% of patients had a high disease burden evaluated with the Durie-Salmon staging system. Overall, 627 infections were recorded (37% of all cases). One hundred and sixty-six patients, accounting for 295 cases (17% of all cases), never experienced any infection, including 25 cases treated with high-dose chemotherapy (HD-Chemo) and autologous stem cell transplantation (SCT, 8% of all SCT cases). High-dose chemotherapy was defined as melphalan at the doses of 200 mg/m^2 or 140 mg/m^2 (for autologous SCT) or as fludarabin (120–150 mg/m^2) and anti-thymocyte globulin (30 mg/kg) plus melphalan (140 mg/m^2) or treosulfan (42 g/m^2) for patients treated with allogeneic SCT. Of cases receiving HD-Chemo and SCT, 296 were treated with autologous SCT and 14 with

Table 1 Patients' characteristics

	All patients	Group EARLY 2003–2008	Group LATE 2009–2015	*p* value
	N = 479	*N* = 182	*N* = 297	
Sex				
Male (%)	272 (57)	101 (56)	171 (58)	0.655
Female (%)	207 (43)	81 (44)	126 (42)	
Age at diagnosis (range)	62 (35–89)	62 (35–86)	62 (41–89)	0.133
Comorbidities [a]				
Cardiac disease [b] (%)	86 (18)	31 (17)	55 (19)	0.681
Diabetes mellitus type II (%)	80 (17)	32 (18)	48 (16)	0.686
Respiratory disease [c] (%)	49 (10)	14 (8)	35 (11)	0.151
Stroke/TIA (%)	33 (7)	15 (8)	18 (6)	0.306
Hepatitis/Liver cirrhosis (%)	11 (2)	5 (3)	6 (2)	0.755
Renal impairment[d]	96 (20)	45 (25)	51 (17)	0.045
Durie-Salmon Stage				
I A/B (%)	77/5 (16/1)	32/2 (18/1)	45/3 (15/1)	0.477
II A/B (%)	25/8 (5/2)	3/0 (2/0)	22/8 (7/3)	< 0.001
III A/B (%)	297/67 (62/14)	116/29 (64/16)	181/38 (61/13)	0.140
MM isotype				
IgG (%)	255 (53)	99 (54)	156 (53)	0.690
IgA (%)	85 (18)	33 (18)	52 (18)	0.862
IgM (%)	4 (1)	2 (1)	2 (1)	0.637
IgD (%)	3 (1)	1 (1)	2 (1)	1.000
BJ (%)	48 (10)	8 (4)	40 (13)	0.001
Asecretory (%)	12 (3)	4 (2)	8 (3)	1.000
Unknown (%)	72 (15)	35 (19)	37 (13)	0.044
Bone disease				
No lesions (%)	92 (19)	31 (17)	61 (21)	0.359
Single lesion (%)	30 (6)	12 (7)	18 (6)	0.803
Multiple lesions (%)	357 (76)	139 (76)	218 (73)	0.489
Days between therapy start and first infection (range)	11 (−152–2954)	12 (0–2954)	11 (−152–854)	0.046

TIA transient ischemic attack

[a] More than 1 comorbidity per patient is possible

[b] Including coronary heart disease and cardiac insufficiency

[c] Including chronic obstructive pulmonary disease and asthma

[d] Any grade of renal impairment according to the KDIGO

allogenenic SCT. As only 14 cases in our series were treated with allogeneic SCT, these cases were not treated separately in the statistical analysis but all patients receiving HD-Chemo were grouped together.

More infection could be identified during the same case; each infection, irrespective in which case it occurred, was defined as a different infectious episode (also called only episode).

The most frequent infection was pneumonia (24% of cases), followed by bacteremia, urinary tract infections, and central venous catheter infections (20%, 20%, and 7% of cases, respectively). During the first infectious episode, the most frequently isolated microorganisms were CNS (43%) followed by *Escherichia coli* (*E. coli*, 18%) and *Enterococci* (11%). *Staphylococcus aureus* (*S. aureus*) was isolated in about 5% of first infectious episodes. During the second infection, *E. coli* was found in 25% of cases, CNS and *Enterococci* in 13% of cases, and *S. aureus* and *Pseudomonas aeruginosa* in 8% of cases each. CNS, *S. aureus*, and *Pseudomonas aeruginosa* were the most frequently isolated microorganisms if a third infectious episode occurred (15% each). The major sources of microorganism isolation were blood culture (in 48% of isolations), urine (20%), central venous catheter (14%), and stool (7%).

Overall, 122 bacteremia with isolation of microorganism from blood culture were reported. In most cases, bacteremia occurred only once per case, although in three patients, two different episodes were documented during the same case. In nine episodes, more than one microorganism was detected during the course of the infection. Two patients, both receiving treatment with bortezomib and dexamethasone, developed a candidemia by *Candida glabrata* and *Candida albicans*, respectively, during a CNS bacteremia. *S. aureus* was isolated in nine episodes, including four identifications of methicillin-resistant *S. aureus* (MRSA). Microorganisms causing bacteremia are summarized in Fig. 1.

One hundred and fifty-three pneumonias were diagnosed in 133 cases. A microorganism causing pneumonia could be isolated in the bronchoalveolar lavage (BAL) or in the sputum in 25 of these episodes. The most frequently isolated bacteria were *Klebsiella pneumoniae* or *oxytoca* (24%, six cases) and *E. coli* (20%, five cases). In six episodes, pneumonia was associated with the diagnosis of influenza, either by influenza A (four cases) or influenza B (two cases) virus. *Pneumocystis jirovecii* pneumonia was documented in two episodes, both occurring in cases receiving long-term treatment with bendamustine and prednisolone. In one of these cases, *Pneumocystis jirovecii* pneumonia was identified as the cause of death.

We recorded 21 episodes of *Clostridium difficile* (*C. difficile*) enteritis (3.4% of all infections); eight episodes each were reported during HD-Chemo or long-term treatment, while three developed during induction treatment. Two patients (one receiving induction with high-dose dexamethasone and one long-term treatment with bendamustine and prednisolone) presented with two different infective episodes during the same patient-case. Two additional patients developed *C. difficile* enteritis without receiving any MM-specific therapy.

In about 30% of episodes, the source of the infection could not be identified and these episodes were classified as fever of unknown origin (FUO).

At the time of last follow-up, 144 patients (30%) had died. An infection was the second major cause of death (45 patients, 31%) after MM disease progression (63 patients, 44%). Twenty-four patients (16%) died of causes other than MM or infection, while in 12 patients, the cause of death was unknown.

Differences according to occurrence of infections and disease stage

We compared the characteristics of patients never experiencing any infections with those of patients reporting at least one infective episode. Patients' characteristics of these two groups are summarized in Supplementary Table 1. Patients experiencing infections had an earlier age at MM diagnosis (61 vs. 67 years, $p < 0.001$), with a higher Durie-Salmon stage (stage III 87% vs. 56%, $p < 0.001$) and a higher number of bone lesions (multiple bone lesions 20% vs. 10%, $p = 0.003$). As could be expected due to the competing risk, patients without infections died on average at an older age as compared to patients with infections (73 years vs. 64 years for patients without and with infections, respectively, $p < 0.001$).

Thirty-five percent of patients with newly diagnosed MM experienced at least one infection, while the corresponding percentages for patients with first, second, and third disease progression were 40%, 48%, and 41%, respectively. During the first infectious episode, the most frequent diagnosis in newly diagnosed patients was FUO (34%), followed by central venous catheter infections (18%) and bacteremia (16%). Relapsed patients had pneumonia (30%, 23%, and 29% in first, second, and third relapse, respectively) and urinary tract infections (13%, 30%, and 32% in first, second, and third

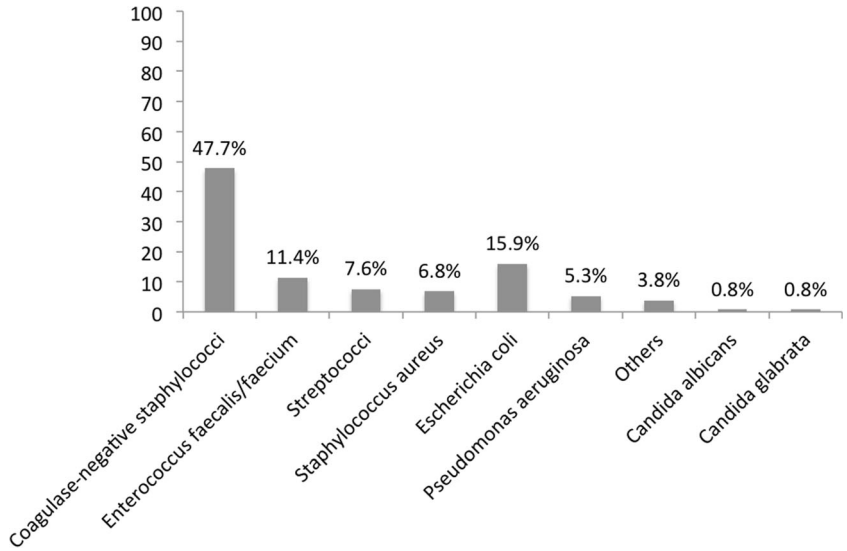

Fig. 1 Microorganisms associated with bacteremia. Numbers indicate percentages. More than one microorganism during the same bacteremic episode is possible. Microorganisms were isolated from blood culture

relapse, respectively) more frequently. FUO was diagnosed in 13% to 18% of relapsed patients.

Rate of infections according to year of case and therapy received

To further assess the impact of novel agents on development of infections, patients were categorized in two groups according to the year when their therapy was administered (between 2003 and 2008, group EARLY, when the availability of novel agents was limited, or between 2009 and 2015, group LATE, when IMiDs and PIs were more widely available). Demographic and disease characteristics were well balanced between the two groups, with the exception of renal insufficiency (higher in patients of group EARLY) and patients with Durie-Salmon stage II (higher in group LATE). More patients diagnosed after 2008 had a Bence Jones myeloma, and in a higher number of patients of group EARLY, myeloma isotype was not available (Table 1). In the overall population, the median time between start of therapy and first infection was 11 days (range −152–2954 days; 12 days (range 0–2954) in group EARLY and 11 days (range −152–854) in group LATE, $p = 0.046$, Table 1). Note that the start of treatment was delayed due to an infection in 18 cases (all group LATE) resulting in "negative days". Thirty-six percent of cases in group EARLY and 38% of cases in group LATE had at least one infection. There was no evidence for a difference in terms of frequency of bacteremia, sepsis, or pneumonia between the groups (Table 2).

To analyze the effect of treatment on infection development, we first categorized cases according to treatment phase, identifying four groups: induction therapy (30% of cases), mobilization chemotherapy (14%), HD-Chemo with SCT (both autologous and allogeneic SCT 18%), and long-term treatment (32%). This last category included all cases receiving long-term treatment irrespective of whether the treatment contained novel agents. Similarly, the category induction therapy included all types of induction irrespective of the use of novel agents, although their use significantly increased after 2009 ($p < 0.001$, Supplementary Table 2). Cases treated only with supportive treatment were not included in this analysis. Cases receiving HD-Chemo with SCT and those treated with long-term therapy had the highest rate of infections (79% and 32%, respectively). Induction therapy was the category with the lowest rate of infections (24%). Infections that develop during induction therapy occurred usually early in the course of treatment, with a median time from start of induction to first infection of 19 days (range 22–237). Conversely, infections in the long-term group arose later during treatment, with a median time to development of 35 days (range 152–2954, $p < 0.001$, Fig. 2.)

Of the cases treated with autologous SCT, 79% developed an infection, whereas in cases receiving allogeneic SCT, the rate was 93%. Infections were mainly of bacterial origin, accounting for 92% and 78% of episodes in which a microorganism was isolated for autologous and allogeneic SCT, respectively. Viral infections were rare, being reported in 13 episodes treated with autologous SCT and 3 episodes receiving allogeneic SCT. More cases receiving allogeneic SCT developed a second infection (10% vs. 50% for autologous and allogeneic SCT, respectively). During the first infective episode and considering only the main diagnosis of the 310 cases treated with SCT, the major cause of infection was bacteremia (26% of episodes), followed by infections of central venous catheter (22%) and pneumonia (9%). The corresponding percentages in cases treated with autologous or allogeneic SCT were 25% and 39% for bacteremia, 23% and 15% for central venous catheter infection, and 8% and 15% for pneumonia, for autologous and allogeneic SCT, respectively. In these episodes, microbiological isolation mainly showed gram-positive bacteria (86% of all episodes) both in cases treated with autologous SCT (86% of cases with a microbiological isolation) and in those receiving allogeneic SCT (89% of cases).

To analyze more in-depth the effect of novel agents (IMiDs and PIs) on the rate and type of infection, we also categorized the cases according to the class of drug administered (Table 3). PIs (either as part of induction or as long-term treatment) were

Table 2 Rate of main infections according to the year of diagnosis

Infection	Group EARLY 2003–2008 (570)	Group LATE 2009–2015 (1120)	OR (95% CI)	*p* value
	N (%)	*N* (%)		
Any infection	206 (36)	421 (38)	1.1 (0.9–1.3)	0.571
Only one infection	166 (29)	345 (31)	1.1 (0.9–1.3)	0.479
Two infections	29 (5)	58 (5)	1.0 (0.6–1.6)	0.940
Three infections	11 (2)	18 (2)	0.8 (0.3–2.3)	0.719
Pneumonia[a]	43 (8)	90 (8)	1.1 (0.7–1.6)	0.735
Bacteremia[a]	32 (6)	87 (8)	1.4 (0.9–2.2)	0.134
Sepsis	9 (2)	27 (2)	1.5 (0.7–3.3)	0.264
Varicella zoster virus	22 (4)	15 (1)	0.3 (0.2–0.6)	0.001

[a] When more than one infection was recorded, only the main diagnosis was considered

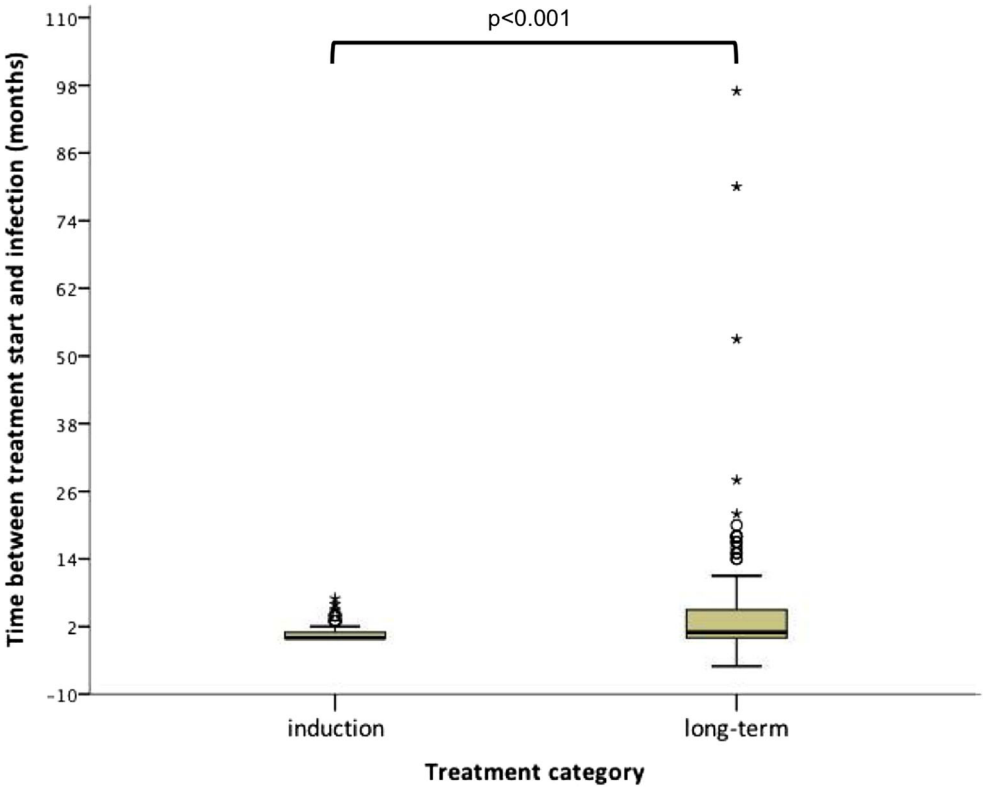

Fig. 2 Time between treatment start and infection development in patients receiving induction and long-term treatment, respectively. Note that both the Wilcoxon-Mann-Whitney tests (which does not address the within patient clustering) as well as a parametric linear model with robust variance estimation which addresses the clustering generalized led to a p value < 0.001

administered in 443 cases (26%), IMiDs (either as part of induction or as long-term treatment) in 229 cases (13%), and a combination of both in 13 (0.8%) patients. Sixty-one cases (4%) received long-term treatment with steroids or interferon alpha. The remaining cases were treated with conventional chemotherapy (including treatment for stem cell mobilization, 31%), SCT (18%), or received only supportive care without active MM treatment (6%). Across all treatment modalities, the most frequent causes of infection were respiratory tract infections (including upper respiratory tract infection and pneumonia) and bacteremia (Table 3).

Varicella zoster reactivation

VZV reactivation was diagnosed in 37 patients (8% of all patients and 2% of all cases). No case of multiple VZV reactivations in the same patient was recorded. Seven patients received conventional chemotherapy, 14 received HD-Chemo + SCT (13 autologous and 1 allogeneic), 10 and 2 patients were treated with PI and IMiDs, respectively. Of the remaining four patients, two developed VZV reactivation without receiving any specific MM treatment, and one patient each was treated with high-dose dexamethasone and interferon alpha. There was no evidence for a difference in the rate of VZV reactivation according to treatment administered (Table 3). In two patients (one with relapsed MM and one with newly diagnosed MM), VZV reactivation preceded the start of treatment by 19 and 9 days, respectively. Median time between start of any treatment and VZV reactivation was 48 days (range 19–1316 days). When looking at patients who received SCT, the median time between chemotherapy start and VZV reactivation was 6 months (range 0–44 months), with four patients developing VZV more than 1 year after autologous SCT. VZV reactivations were more frequent in patients treated between 2003 and 2008 (4% vs. 1% for group EARLY and group LATE, respectively, $p = 0.001$, Table 2). Conversely, there was no evidence of a difference in the time between treatment start and VZV reactivation between group EARLY and LATE, both when looking at the all patients (66 vs. 44 days for group EARLY and group LATE, respectively, $p = 0.283$) or for the subgroup of patients after SCT (6 months for group EARLY and LATE, respectively, $p = 0.456$). Acyclovir was the most commonly used antiviral therapy (79% of cases), for a median length of treatment of 12 days (range 6–100 days). There was no evidence for a difference in the length of antiviral therapy between group EARLY and group LATE (10.5 vs. 13 days, ranges 7–100 days and 6–55 days for group EARLY and group LATE, respectively, $p = 0.963$), and none for the number of patients who switched antiviral agents (10 cases, 27%, 4 in group EARLY and 6 in group LATE, $p = 0.142$).

Risk factors associated with infection development

In univariate analysis, variables associated with a higher risk of infection were a relapsed disease, the presence of anemia

Table 3 Rate of infections according to treatment received (called patient-cases in the main text)

	Conventional chemotherapy[a] (*N* = 522) (%)	HD-Chemo (*N* = 310) (%)	PI[a] (*N* = 443) (%)	IMiDs[a] (*N* = 229) (%)	PI + IMiDs[a] (*N* = 13) (%)	Steroid or interferon (*N* = 61) (%)	Supportive therapy (*N* = 112) (%)
No infections	380 (72.8)	64 (20.6)	330 (74.5)	152 (66.4)	7 (53.8)	35 (57.4)	95 (84.8)
Any infection	142 (27.2)	246 (79.4)	113 (25.5)	77 (33.6)	6 (46.1)	26 (42.6)	17 (15.2)
Only one infection	124 (23.8)	210 (67.7)	84 (18.9)	54 (23.6)	6 (46.1)	19 (31.1)	14 (12.5)
Two infections	15 (2.8)	33 (10.6)	20 (4.5)	13 (5.7)	–	5 (8.2)	1 (0.9)
Three infections	3 (0.6)	3 (1)	9 (2)	10 (4.4)	–	2 (3.3)	2 (1.8)
Bacteremia	18 (3.5)	67 (21.6)	15 (3.4)	14 (6.1)	–	6 (9.8)	2 (1.8)
Pneumonia	34 (6.5)	31 (10)	33 (7.5)	34 (14.8)	1 (7.6)	12 (34)	8 (7.1)
URTI	13 (2.5)	7 (2.3)	18 (4.1)	12 (5.2)	2 (15.4)	6 (9.8)	1 (0.9)
CVC-infection[b]	5 (1)	80 (25.8)	7 (1.6)	6 (2.6)	1 (7.6)	4 (6.6)	–
Other CDI	61 (11.7)	45 (14.5)	58 (13.1)	42 (18.3)	1 (7.6)	14 (23)	8 (7.1)
Fungemia	–	–	2 (0.5)	–	–	–	–
VZV reactivation	7 (1.3)	14 (4.5)	10 (2.3)	2 (0.9)	–	2 (3.3)	2 (1.8)
BONJ	–	–	4 (1)	3 (1.3)	–	–	–
FUO	52 (10)	86 (27.7)	29 (6.5)	17 (7.4)	2 (15.4)	–	1 (0.9)

HD-Chemo high-dose chemotherapy, *PI* proteasome inhibitors, *IMiDs* immunomodulatory drugs, *URTI* upper respiratory tract infection, *CVC* central venous catheter, *CDI* clinical documented infections, including tissue infection, urinary tract infections, endocarditis, gastroenteritis, and meningitis; VZV: Varicella zoster virus; BONJ: bisphosphonate associated osteonecrosis of the jaw, *FUO* fever of unknown origin

[a] The use of PIs and IMiDs during induction increased after 2009. Sixty-seven percent (138/205) of cases treated between 2009 and 2013 received induction with conventional chemotherapy, in contrast with only 13% of those treated after 2009. The correspondent percentages for PI and IMiDs are 23% and 85% for cases treated before and after 2009, respectively. See also Supplementary Table 2

[b] All cases treated with HD chemo had a CVC, while in the other groups, most patients did not have a CVC

before the start of treatment, bone marrow plasma cell burden higher than 70%, multiple bone lesions at diagnosis (whether first diagnosis or relapse), and treatment with HD-Chemo with SCT (Table 4). Neither the period when treatment was given nor age, sex, hypercalcemia, renal insufficiency, and use of IMiDs or PI were significantly associated with infections.

In multivariate analysis, the following factors retained an independent prognostic value for the development of infections: relapsed disease (OR 2.3, 95% CI 1.5–3.4, $p < 0.001$), anemia (OR 1.4, 95% CI 1.1–2.0, $p = 0.02$), bone marrow plasma cell infiltration > 70% (OR 1.5, 95% CI 1.1–2.1, $p = 0.01$), and treatment with HD-Chemo and SCT (OR 10.7, 95% CI 7.0–16.3, $p < 0.001$) (Table 4).

Discussion

Patients with MM experience a higher rate of infections compared to the general population and infections are one of the main causes of early death in MM patients [14]. Whether rate and type of infections have changed since the advent of novel agents is still a matter of debate [15, 17, 19, 20]. Treatment with PIs has been linked to a higher risk of developing a reactivation of VZV [16], and recently, a high tumor load has been identified as a risk factor for the development of blood stream infection [21]. In contrast to other authors who showed an increased risk of infection in patients diagnosed in the more recent years [15], our data show that the risk of infection remained rather constant during the years. It has to be noted, however, that previous studies included patients diagnosed until 2004, while our data include patients diagnosed from 2003 until 2015, when the use of HD-Chemo was already a standard of care for younger patients. Nevertheless, we failed to demonstrate an increased risk of infection in patients treated with novel agents, showing a constant rate of infections in patients treated before and after 2009. In accordance with what was already reported by other groups [15, 17], the higher rate of infection was seen in patients receiving HD-Chemo with SCT, confirming that deep and long-term neutropenia following high-dose chemotherapy is the major risk factor for infection's development. We were also able to confirm that infections are associated with disease burden and disease state. A high disease burden at diagnosis (identified as PC infiltration in the bone marrow and the presence of anemia) and relapsed disease were risk factors for a higher rate of infection in the univariate analysis and retained their prognostic value in the multivariate analysis.

The lowest rate of infection was seen in patients who received induction treatment. Infections during induction developed earlier than those occurring in patients who received long-term therapy, and were mainly early events in the course of treatment. It is likely that in most cases, the infection

Table 4 Factors associated with the presence of an infection from logistic regressions with generalized estimating equations. Effect size estimates (with 95% confidence interval (CI)) are provided such that odds ratios > 1 indicate higher odds for an infection (usually) in the presence of a factor. The reference category or unit is provided in square brackets

Factors associated with the presence of infections	Univariate models[a]		Multivariable model[a,b]	
	crude odds ratio (95% CI)	*p* value (two-sided)	adjusted odds ratio (95% CI)	*p* value (two-sided)
Relapse [absent]	1.4 (1.1–1.7)	0.008	2.3 (1.5–3.4)	< 0.001
Anemia [absent]	1.4 (1.1–1.8)	0.004	1.4 (1.1–2.0)	0.02
BM PC > 70% [absent]	1.5 (1.1–1.9)	0.002	1.5 (1.1–2.1)	0.01
Multiple bone lesions [absent]	1.8 (1.3–2.4)	< 0.001	1.3 (0.8–2.2)	0.24
Treatment [other treatment[c]]				
HD-Chemo	9.5 (6.8–13.1)	< 0.001	10.7 (7.0–16.3)	< 0.001
Treatment with PI	0.9 (0.7–1.1)	0.33	0.8 (0.6–1.2)	0.30
IMiDs alone	1.2 (0.9–1.7)	0.16	1.0 (0.7–1.5)	0.96

BM PC bone marrow plasma cells, *HD-Chemo* high-dose chemotherapy, *PI* proteasome inhibitors

[a] Estimates are derived from complete case analyses

[b] This model includes all factors from the univariate analyses

[c] Covers conventional chemotherapy and steroid or interferon treatment

preceded the effects of induction treatment on disease burden, thus strengthening the importance of disease burden in influencing the risk of development of infections.

In this patient population, the rate of VZV reactivation was comparable to the rates expected in MM patients not receiving PI treatment [16]. We did not observe any increase of viral complication and VZV reactivation in patients treated with PI. Conversely, VZV reactivation was more frequent in those patients treated before 2009, when PIs were not widely available. It has to be noted, however, that due to the known increased risk of VZV reactivation associated with PI therapy, patients treated with PI received prophylaxis with aciclovir in doses ranging from 400 to 1200 mg per day. The administration of standard prophylaxis might have reduced the incidence of VZV in this patients' group and is likely to explain our findings. Furthermore, we were able to demonstrate that the reactivation of VZV can be a late complication after SCT. In our retrospective cohort, 5% patients who received HD-Chemo with SCT developed VZV reactivation late after SCT, with a median time from SCT to VZV reactivation of 6 months (range 0–44 months). In accordance with the current guidelines of the German Society for Hematology and Medical Oncology (DGHO) [22], our patients did not routinely receive long-term antiviral prophylaxis after SCT, and we could not see any difference in the rate of VZV reactivation after SCT according to treatment period. These data (a low incidence of PI-associated VZV reactivation with acyclovir prophylaxis and late development of VZV reactivation after SCT) strengthen the argument for a longer VZV prophylaxis (at least 1 year after SCT) in MM patients.

Patients developing infections were younger than those not developing an infection. This finding is not surprising, considering that younger patients are more likely to receive HD-Chemo with SCT, and treatment with HD-Chemo was confirmed to be an independent risk factor for infection development. As expected, patients who developed infections died on average at a younger age, thus confirming that infections are one of the major causes of death in myeloma patients.

In conclusion, this analysis reveals that, with the appropriate prophylaxis and supportive care, the administration of novel agents is not linked to a higher risk of developing infection or to a different infection epidemiology. VZV reactivation can be a late complication after SCT and should not be underestimated. High-dose therapy and high disease burden remain major risk factors for infection, warranting a risk-adapted infection prophylaxis after HD-chemo with SCT and effective strategies to rapidly induce remission. In summary, despite the advances made in the recent years in myeloma treatment and supportive care, still about 60% of patients will develop at least one infection during the course of treatment. A close patient monitoring and more effective strategies to prevent this potentially lethal complication are urgently needed in the quest for curing multiple myeloma.

Authors' contributions AB performed analysis and wrote the paper, MK collected data and performed analysis, AS performed analysis, MvLT designed the research and wrote the paper, SS, IH, TE, HS, OY, KS, LOM, AH provided patients data and important intellectual input. All authors reviewed and gave the final approval to the paper.

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Compliance with ethical standards

Ethical approval and informed consent The present study was conducted after approval by the institutional review board at Jena University Hospital in Germany. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. As data analyzed were pseudonimized data normally collected during clinical practice, the responsible ethic committee was of the opinion that no extra informed consent was needed for the present research.

Conflict of interest AB: Honoraria: Celgene, Takeda, Travel support: Janssen, Celgene, Takeda, Research support: Celgene; IH: Research support: Medac, Novartis, Travel support: Medac, Novartis, Gilead; LOM: Research support: Celgene, Honoraria: Celgene, Janssen, Novartis, Amgen, Bristol Myers Squibb; MvLT: Honoraria: Janssen, Celgene, Novartis, Takeda, Travel support: Janssen, Celgene, Novartis, Takeda, Research support: Janssen, Celgene, Novartis, Takeda; the other authors have no relevant conflict of interest to disclose.

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