Original Article

Partial immunoparesis contributes to risk of early infections in patients with multiple myeloma

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Background: Partial immunoparesis, which means at least two suppressed uninvolved immunoglobulins (Igs), had been reported to be associated with poor prognosis in patients with multiple myeloma (MM), but the impact on early infections remains unknown. The purpose of our study was to determine the prognostic implications of partial immunoparesis on early grade ≥3 infections in patients with MM.

Methods: Herein we retrospectively analyzed the clinical data of 123 MM patients between 2012 and 2020 at Nanfang Hospital. All patients received bortezomib-based regimens. The relationship between early grade ≥3 infections and partial immunoparesis was investigated using Cox regression analysis.

Results: Our data showed partial immunoapresis was found in 63% MM patients. Partial immunoparesis was significantly related to elevated beta-2-microglobulin (B2M), decreased estimated glomerular filtration rate (eGFR) and progressive international staging system (ISS) stage (P<0.05). Especially, univariate Cox regression analysis showed partial immunoparesis was significantly correlated with early grade ≥3 infections (P=0.003). Moreover, multivariate Cox regression analysis showed partial immunoparesis was an independent significant prognostic factor for early grade ≥3 infections [odds ratio (OR) =3.048; 95% confidence interval (CI): 1.429–6.504; P=0.004]. Furthermore, partial immunoapresis could improve the infection risk model built by Dumontet *et al.*

Conclusions: Our study showed that partial immunoparesis could predict early infections in patients with MM, which may be used to identify the high risk patients for infections and guide strategies for infection prevention.

Keywords: Immunoparesis; infection; multiple myeloma (MM); prediction

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Introduction

The survival of multiple myeloma (MM) patients have been improved by the wide use of novel drugs and autologous stem cell transplantation (1). However, due to high incidence of early mortality (2-4), about 10% patients couldn't reap the benefits of them. Infections were the most common direct cause of early mortality, Augustson *et al.* (3) reported that infections contributed to almost 50% of early mortality and this rate was 65% in the study conducted by Hsu *et al.* (2). Meanwhile, infections also contribute to diseases progression through various mechanisms, such as production of interleukin-6 (5-7) and activation of Toll-like receptor signaling pathways (8,9). Thus, infections impose a major threat to patients with MM and there is an urgent clinical need for infections prediction and prevention.

Currently, two risk scoring system had been developed to predict the risk of early grade ≥3 infections in patients with MM. Dumontet *et al.* (10) built a predict model including

Eastern Cooperative Oncology Group-performance status (ECOG-PS), beta-2-microglobulin (B2M), lactate dehydrogenase (LDH) and hemoglobin levels. The high risk MM patients defined as 2 to 5 scores showed significantly higher rate of infections than the low risk patients (24.0% *vs.* 7.0%). However, the study only included patients treated with lenalidomide-based regimens. Valkovic *et al.* (11) had proposed the multiple myeloma index for risk of infection (MMIRI), with a sensitivity of 93.2% and specificity of 80.2%. But this model was too complicated to be widely applied in clinical practice. It's urgent and necessary to explore new simple and useful markers for predicting infections in MM.

Normal immunoglobulins (Igs) play an important role in adaptive immune response to infections. In MM patients, normal plasma cells were inhibited by the rapidly proliferation of malignant plasma cells which causes immunoparesis and makes patients vulnerable to infections (12). Immunoparesis means at least one suppressed uninvolved Igs. Partial immunoparesis, which means at least two suppressed uninvolved Igs, had been shown to correlate with inferior clinical features and outcomes in MM patients (13-15). However, the correlation between immunoparesis and early infections in MM remained unclear. Herein we investigated the value of partial immunoparesis in predicting risk of early grade ≥3 infection in MM patients.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-1627).

Methods

We reviewed medical records from 123 newly diagnosed MM patients, according to IMWG criteria (16), between 2012 and 2020 at Nanfang Hospital. Patients diagnosed as solitary osseous MM, solitary extra-osseous MM and smoldering MM were excluded from this study. Patients that had biopsy proven organ involvement with light-chain (AL) amyloidosis at diagnosis or during the follow-up period were also excluded. All patients received bortezomib-based regimens. Sixty percent (74/123) received bortezomib and dexamethasone plus cyclophosphamide (VCD), 29% (36/123) received bortezomib and dexamethasone plus thalidomide (VDT), 11% (13/123) received bortezomib and dexamethasone plus doxorubicin (PAD). Among them, 10% (12/123) patients received autologous stem cell transplant (ASCT). Valacyclovir was taken as anti-viral prophylaxis. No antibiotic prophylaxis was used. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The current study protocol was approved by the Ethics Committee of Southern Medical University Nanfang Hospital, Guangzhou, China (No. NEFC-2020-R391). All patients gave written informed consent themselves prior to treatment allowing the use of their medical records for medical research.

ECOG-PS, hemoglobin, neutrophil, lymphocyte, B2M, albumin, LDH, corrected calcium (cCa), C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR) (17), international staging system (ISS), revised ISS (R-ISS) (18), and chromosomal abnormalities [t(4;14), t(11;14), t(14;16), del17p13, del13q14, t(14;20), t(8;14)] were assessed at diagnosis. Immunoparesis was defined as reduction of an uninvolved Ig below the lower limit of normal for our laboratory reference range, which for IgG was <7 g/L, for IgA was <0.7 g/L and for IgM was <0.4 g/L. Partial immunoparesis was defined as at least two suppressed uninvolved Igs. Hematologic adverse events (AEs) included neutropenia, thrombocytopenia. All AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Cumulative incidences of grade ≥3 hematologic AEs, non-hematologic AEs were calculated from the time of treatment start until the date of first toxicity due to causes other than progression or death. Early grade ≥3 infections correspond to the first grade ≥3 infections during the first 4 months.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Sciences version 22.0 for Windows. Continuous data were described with median and interquartile range (IQR). The χ^2-test and Fisher's exact test were applied to assess the differences in nominal variables. Cumulative incidences were estimated by Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate modeling were conducted by the Cox regression analysis. P<0.05 was considered to be statistical significance.

Results

Patient characteristics

Data from a total of 123 MM patients was retrospectively analyzed. The median follow-up period was 25 months

(IQR: 16–40). The median age at diagnosis was 57 years (IQR: 51–64), which was similar to other recent studies of Chinese MM patients (19-22). According to ISS, 57% (70/123) patients were at stage III. Base on R-ISS, 21% (21/100) patients were at stage III. After induction, 81% (100/123) patients acquired at least partial response and grade ≥3 neutropenia was documented in 21% (26/123) patients.

Immunoparesis was found in 86% (106/123) patients and 63% (78/123) of them were resent with partial immunoparesis in our study. Patients with partial immunoparesis had significantly elevated B2M (P<0.001), lower eGFR (P=0.004) and advanced ISS stage (P<0.001). There were no differences in response, neutropenia between patients with and without partial immunoparesis (P>0.05). Among 12 transplanted patients, 10 of them had immunoparesis and 5 of them developed early grade ≥3 infections. Clinical characteristics of patients according to partial immunoparesis were summarized in *Table 1*.

We also found the severity of immunosuppression was associated with early grade ≥3 infections in patients with IgA and IgG MM (Table S1). In IgA MM patients, suppression of IgM (>0% and >50%) and IgG (>25%) were significantly related to infections. In IgG MM patients, suppression of IgA (>0% and >25%) was also significantly related to infections. Although without significance, suppression of IgM (>50%) tended to have higher infection rates (64% *vs.* 46%). However, no significant association between the severity of immunosuppression in light chain only MM.

Partial immunoparesis and first early grade ≥3 infections

During the follow-up, 45% (55/123) patients presented at least one grade ≥3 infection, the median time from diagnosis to the development of early grade ≥3 infection was 22 days (IQR: 10–70). At the first 4 months, 39% (48/123) patients presented at least one grade ≥3 infection. Early grade ≥3 infections and grade ≥3 neutropenia at the time of infection were summarized in *Table 2*. The distribution of infections were similar to other study (23). Among them, pneumonia was the most common (70.8%). The therapeutic regimens and grade ≥3 neutropenia were shown in Table S2. Cause the regimens were all bortezomib-based, the incidences of infections were similar (P=0.056). No significant correlation between early grade ≥3 neutropenia and early grade ≥3 infections was found (P=0.249). Patients with early grade ≥3 infections were correlated with poor response (P=0.008).

Univariate Cox regression analysis showed partial immunoparesis, ECOG-PS, NT-proBNP, B2M, hemoglobin, eGFR, LDH and ISS stage III were correlated with first grade ≥3 infections (Table S3). Patients with partial immunoparesis significantly had high risk of early grade ≥3 infections (P=0.002, with 4 months cumulative incidence of 50.0% *vs.* 20.0%, *Figure 1A*). Multivariate Cox regression analysis revealed partial immunoparesis as an independent significant prognostic factor for first grade ≥3 infections [odds ratio (OR) =3.048; 95% confidence interval (CI): 1.429–6.504; P=0.004] of ECOP-PS, NT-proBNP and hemoglobin (*Table 3*).

In our study, high and low risk defined by the predictive model built by Dumontet *et al.* (10) showed significantly different rates of infection (P=0.001, with 4 months cumulative incidence of 50.7% *vs.* 22.0%, *Figure 1B*). To found out whether partial immunoparesis could improve the risk model of Dumontet *et al.* (10), we explored the prognostic value of partial immunoparesis in low/high risk groups defined by Dumontet *et al.* (10). Partial immunoparesis could identify a subgroup of patients with higher infection risk in the high risk group defined by Dumontet *et al.* (10) (P=0.037, with 4 months cumulative incidence of 57.9% *vs.* 25.0%, *Figure 1C*). However, partial immunoparesis failed to separate the low risk group defined by Dumontet *et al.* (10) into two subgroups (P=0.415, with 4 months cumulative incidence of 28.6% *vs.* 17.2%, *Figure 1D*).

Discussion

Partial immunoparesis had been shown to correlate with inferior clinical features and outcomes in MM patients (13-15). However, the correlation between partial immunoparesis and early infections in MM remained unknown. In this study, we retrospectively explored the impact of partial immunoparesis on the early infections in patients with MM. Our data showed that partial immunoparesis at diagnosis was related to early grade ≥3 infections.

In our study, immunoparesis was observed in 86% patients of patients and partial immunoparesis in 63% patients. Similar to our study, previous studies showed that immunoparesis could be detected in 84–94% patients and partial immunoparesis could be detected in 65–81% patients (13-15,24). Until now, studies about partial immunoparesis were rare. In our study, partial immunoparesis was

Table 1 Baseline patient characteristics according to partial immunoparesis at diagnosis

Characteristics	All patients	Partial immunoparesis		P value
		Yes (n=78)	No (n=45)	
Age, ≥65	23 (18.7)	17 (21.8)	6 (13.3)	0.338
Sex, male	70 (56.9)	48 (61.5)	22 (48.9)	0.190
ECOG-PS, ≥2	25 (20.3)	18 (23.1)	7 (15.6)	0.361
Early grade ≥3 infections	48 (39.0)	39 (50.0)	9 (20.0)	0.001
Hemoglobin, <90 g/L	73 (59.3)	48 (61.5)	25 (55.6)	0.570
Neutrophil, $<2\times10^9$/L	24 (19.5)	14 (17.9)	10 (22.2)	0.639
Lymphocyte, $<1\times10^9$/L	11 (8.9)	7 (9.0)	4 (8.9)	1.000
Albumin, <35 g/L	90 (73.2)	58 (74.4)	32 (71.1)	0.833
B2M, ≥3.5 mg/L	95 (77.2)	67 (85.9)	28 (62.2)	0.004
B2M, ≥5.5 mg/L	72 (58.5)	57 (73.1)	15 (33.3)	<0.001
Immune type				0.464
IgG	66 (53.7)	41 (52.6)	25 (55.6)	
IgA	28 (22.8)	16 (20.5)	12 (26.7)	
Light chain only	29 (23.6)	21 (26.9)	8 (17.8)	
cCa, >2.75 mg/L	31 (25.2)	23 (29.5)	8 (17.8)	0.197
eGFR, <60 mL/min/1.73 m^2	49 (39.8)	39 (50.0)	10 (22.2)	0.004
Elevated LDH,	28 (22.8)	17 (21.8)	11 (24.4)	0.824
CRP, ≥5 mg/L	49 (41.2)	33 (43.4)	16 (37.2)	0.564
NT-proBNP, ≥300 ng/L	47 (38.2)	30 (62.5)	17 (22.7)	<0.001
High risk FISH, yes	16 (17.2)	10 (17.9)	6 (16.2)	1.000
ISS				<0.001
I	9 (7.3)	3 (3.8)	6 (13.3)	
II	42 (34.1)	18 (23.1)	24 (53.3)	
III	72 (58.5)	57 (73.1)	15 (33.3)	
R-ISS				0.299
I	6 (6.1)	2 (3.3)	4 (10.5)	
II	70 (71.4)	43 (71.7)	27 (71.1)	
III	22 (22.4)	15 (25.0)	7 (18.4)	
Response to induction therapy (≥ PR)	100 (81.3)	64 (82.1)	36 (80.0)	0.813
Early hematologic AEs (grade ≥3)				
Thrombocytopenia	17 (13.8)	11 (14.1)	6 (13.3)	1.000
Neutrophil, $<1\times10^9$/L	26 (21.1)	17 (21.8)	9 (20.0)	1.000
ASCT	12 (9.8)	10 (12.8)	2 (4.4)	0.207
High risk defined by Dumontet *et al.* (10)	73 (59.3)	57 (73.1)	16 (35.5)	<0.001

Number (%). ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; B2M, beta-2-microglobulin; IgG, immunoglobulin G; IgA immunoglobulin A; cCa, corrected calcium; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; CRP, C-reactive protein; NT-proBNP, N-aimo terminal fragment of the B-type brain natriuretic peptide; FISH, fuorescence in situ hybridization; ISS, international staging system; R-ISS, revised ISS; PR, partly response; AEs, adverse events; ASCT, autologous stem cell transplant.

Table 2 Early grade ≥3 infections and grade ≥3 neutropenia at the time of infection

Types	Number (%)
MDI	
Pneumonia	2 (4.2)
Acinetobacter baumannii	1 (2.1)
Staphylococcus haemolyticus	1 (2.1)
Septicemia	2 (4.2)
Streptococcus bovis type II	1 (2.1)
Herpes zoster	1 (2.1)
CDI	
Pneumonia	32 (66.7)
Bacterial	22 (45.8)
Fungal	4 (8.3)
Bacterial and fungal	6 (12.5)
Colitis	2 (4.1)
Urinary tract infection	2 (4.1)
FUO	8 (16.7)
Neutrophil $<1\times10^9$/L at the time of infection	13 (27.1)

MDI, microbiologically documented infection; CDI, clinical documented infection; FUO, fever of unknown origin.

associated with elevated B2M, decreased eGFR and high ISS scores and was not associated with treatment response, which were similar to a pervious large cohort study (13). Our results were also consistent with a previous study in that the majority of infections occurred during the first 4 months of treatments (10). Most ASCT events were performed after the first 4 months, thus ASCT wasn't a risk factor for early infections (P=1.000, data not shown) in this study.

Currently, two risk scoring systems had been developed to separate patients into high- and low-risk groups for early grade ≥3 infections (10,11). Dumontet *et al.* (10) found ECOG-PS, serum B2M, LDH and hemoglobin levels were independent significant factor in predicting early grade ≥3 infections. However, the study didn't take immunoparesis or partial immunoparesis into consideration. A larger study of 5,826 UK myeloma trial patients showed immunoparesis had no effect on survival in the first few months (25) and several studies (11,26,27) also found there was no association between infections and immunoparesis, but they didn't take partial immunoparesis or levels of polyclonal Igs into consideration. Igs and plasma cells played an important role in the protection against infections, but the prognostic value of partial immunoparesis in infections remained unknown. In our study, patients with partial immunoparesis at diagnosis had significantly high risk of infections. Univariate and multivariate Cox regression analyses suggested the prognostic value of partial immunoparesis in infections was independent of ECOG-PS, serum B2M, LDH and hemoglobin. We also found the partial immunoparesis improved the risk stratification of the predict model built by Dumontet *et al.* (10) in MM patients. In our study, MMIRI wasn't taken into analysis due to lacking of some parameters. Response to treatment and neutropenia were adverse factors that contributes to infections (11,28). *Table 1* showed that the distribution of these two factors had no significant difference between the two groups separated by partial immunoparesis. A pervious large cohort study also showed partial immunoparesis wasn't associated with response (13). As a result, partial immunoparesis may be considered as an independent poor prognostic factor for early grade ≥3 infections in newly diagnosed MM patients.

Neutropenia was associated with infections in MM (11,29). However, in this study we didn't observe significant correlation between grade ≥3 neutropenia and grade ≥3 infections (P=0.249) (Table S2). This result was similar to a previous study (23). Dumontet *et al.* (10) also found nearly 75% of all grade ≥3 infections occurred in the absence of neutropenia in MM patients. We believed this was at least partly due to the administration of recombinant human granulocyte colony-stimulating factors (rhG-CSF), which is common in the treatment of neutropenia. In this study, all patients with grade ≥3 neutropenia received rhG-CSF, which reduced the duration and severity of neutropenia (30,31), thus decreased the significance of correlation between neutropenia and infections.

This study found NT-proBNP was related with early grade ≥3 infections. NT-proBNP was a frailty parameter and was associated with disease severity in MM (32,33). Anemia, renal and cardiac impairments due to deposition of monoclonal light chains were common in MM patients (34). These complications contribute to both high level of NT-proBNP (35-40) and infections (41-43), which underlines the plausibility of the correlation between NT-proBNP and risk of infection in MM patients.

We also found the severity of IgG and IgM suppression

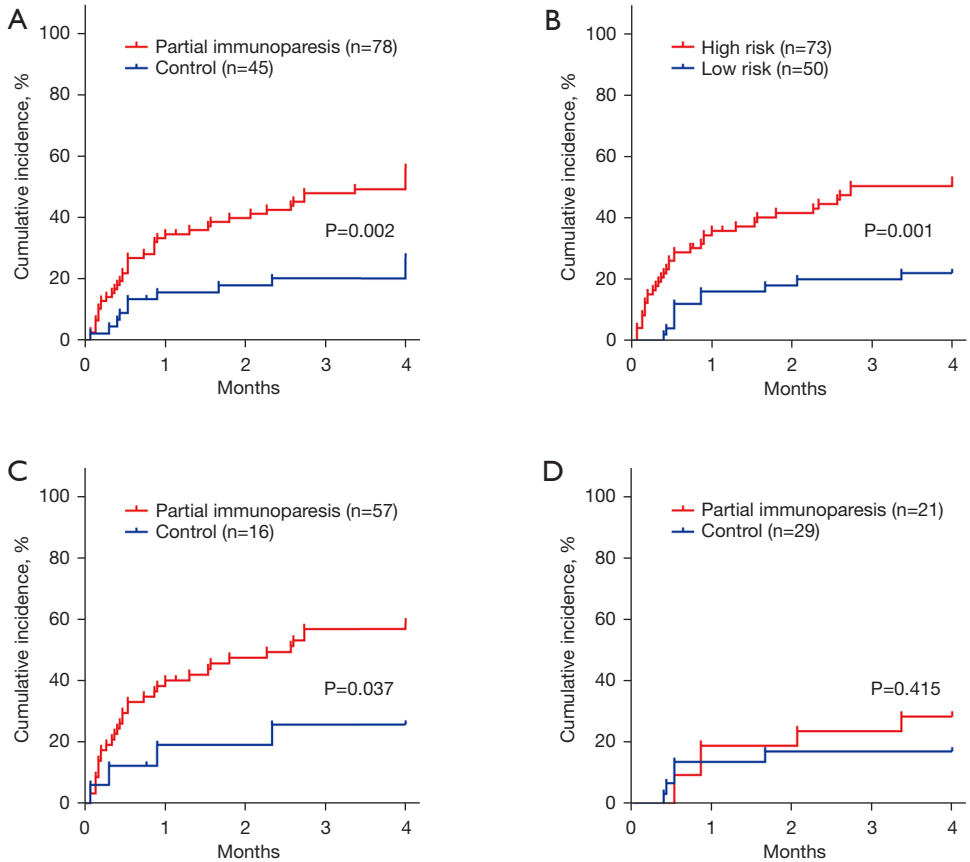

Figure 1 Cumulative incidence of first early grade ≥3 infections according to partial immunoparesis. Cumulative incidence of first early grade ≥3 infections according to partial immunoparesis in the entire group (A), risk groups defined by Dumontet *et al.* (10) (B), high (C) and low (D) risk group defined by Dumontet *et al.* (10).

Table 3 Multivariate Cox regression analysis for grade ≥3 infections

Various	OR	95% CI	P value
ECOG-PS, ≥2	2.754	1.457–5.207	0.002
NT-proBNP, ≥300 ng/L	2.766	1.369–5.591	0.005
Partial immunoparesis	3.048	1.429–6.504	0.004
eGFR, <60 mL/min/1.73 m^2	0.916	0.381–2.201	0.844
B2M, ≥5.5 mg/L	0.698	0.281–1.731	0.438
Elevated LDH	1.402	0.721–2.729	0.319
Hemoglobin, <90 g/L	2.449	1.185–5.063	0.016

OR, odds ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; NT-proBNP, N-aimo terminal fragment of the B-type brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; B2M, beta-2-microglobulin.

was associated with early grade ≥3 infections in IgA MM, suppression of IgA was also significantly related to infections in IgG MM. However, no significant association between the severity of immunosuppression was found in light chain only MM. Currently, the cut-off value of severity of immunosuppression was still controversial. Due to the small number of patients in the study, we couldn't make up a solid conclusion.

There is a broad complexity of immunodeficiency in patients with MM and management of infections represents a clinical challenge. Currently, oral administration of antibiotics is commonly taken in routine clinical practice for prevention of infections. A randomized study of 977 patients found all patients were benefit from prophylactic levofloxacin and suggested prophylactic antibiotics for 4 months (44). Decisions of antibiotic prophylaxis depends on the common pathogens in each region and the course of diseases. We hope our study would guide the accurate use of antibiotic prophylaxis and avoid antibiotic abuse. Antimicrobial prophylaxis and immune enhancement strategies such as vaccination were strongly recommended for patients with partial immunoparesis.

It should be noted that this study was a retrospective study with a relatively small number of patients from a single center and antibiotic prophylaxis was not routine used. However, all the included patients were only bortezomib-based regimens, which could deduce the selection bias. Although similar with other recent studies of Chinese MM patients (19-22), the median age at diagnosis was younger than Western people and few receive intensive treatment or ASCT dues to cost and acceptance of ASCT. Our results need to be verified by future studies.

Conclusions

In summary, we explored the impact of partial immunoparesis on the early infections in patients with MM and found that partial immunoparesis was associated with early grade ≥3 infections. Once we result was confirmed in the prospective study, these patients should receive antibiotic prophylaxis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-1627

Data Sharing Statement: Available at https://dx.doi.org/10.21037/tcr-21-1627

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-1627). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The current study protocol was approved by the Ethics Committee of Southern Medical University Nanfang Hospital, Guangzhou, China (No. NEFC-2020-R090). All patients gave written informed consent themselves prior to treatment allowing the use of their medical records for medical research.

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Supplementary

Table S1 Early grade ≥3 infections according to severity of suppressed uninvolved immunoglobulins

Immune types	Types of suppressed uninvolved Igs	Severity of suppressed uninvolved Igs, %	All patients	Infection, yes	Infection, no	P value
Light chain only	IgG	>0	20 [77]	10 [91]	10 [67]	0.197
		>25	16 [64]	6 [60]	10 [67]	1.000
		>50	5 [20]	4 [40]	1 [7]	0.121
		>75	0	0	0	–
	IgA	>0	18 [69]	6 [55]	12 [80]	0.218
		>25	12 [48]	3 [30]	9 [60]	0.226
		>50	10 [40]	3 [30]	7 [47]	0.678
		>75	4 [16]	2 [20]	2 [13]	1.000
	IgM	>0	18 [69]	8 [73]	10 [67]	1.000
		>25	12 [46]	6 [55]	6 [40]	0.692
		>50	5 [19]	5 [36]	1 [7]	0.128
		>75	0	0	0	–
IgA	IgG	>0	17 [74]	9 [100]	8 [57]	0.048
		>25	15 [65]	8 [89]	7 [50]	0.086
		>50	10 [44]	7 [78]	3 [21]	0.013
		>75	3 [13]	2 [22]	1 [7]	0.538
	IgM	>0	18 [82]	9 [100]	9 [69]	0.115
		>25	12 [57]	8 [89]	4 [33]	0.024
		>50	9 [43]	6 [67]	3 [25]	0.087
		>75	2 [10]	1 [11]	1 [83]	1.000
IgG	IgA	>0	42 [66]	19 [86]	23 [55]	0.013
		>25	29 [45]	15 [68]	14 [33]	0.010
		>50	22 [34]	11 [50]	11 [26]	0.095
		>75	6 [9]	3 [14]	3 [7]	0.406
	IgM	>0	51 [77]	18 [82]	33 [75]	0.757
		>25	46 [70]	17 [77]	29 [66]	0.405
		>50	34 [52]	14 [64]	20 [46]	0.198
		>75	15 [23]	7 [32]	8 [18]	0.229

Number [%]. Ig, immunoglobulin.

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Table S2 Therapeutic regimens, grade ≥3 neutropenia and grade ≥3 infections

Various	Infection, no	Infection, yes	P value
Therapeutic regimens			0.056
VCD	50 (67.6)	24 (32.4)	
PAD	9 (69.2)	4 (30.8)	
VDT	16 (44.4)	20 (55.6)	
Neutrophil $<1\times10^9$/L			0.258
No	62 (63.9)	35 (36.1)	
Yes	13 (50.0)	13 (50.0)	
Response to induction therapy (≥ PR)			0.008
Yes	67 (67.0)	33 (33.0)	
No	8 (34.8)	15 (65.2)	

Number (%). VCD, bortezomib and dexamethasone plus cyclophosphamide; PAD, bortezomib and dexamethasone plus doxorubicin; VDT, bortezomib and dexamethasone plus thalidomide; PR, partly response.

Table S3 Univariate Cox regression analysis for early grade ≥3 infections

Various	OR	95% CI	P value
Age, ≥65	0.971	0.470–2.004	0.936
Sex, male	1.423	0.788–2.572	0.242
ECOG-PS, ≥2	3.576	1.994–6.411	<0.001
NT-proBNP, ≥300 ng/L	3.971	2.207–7.147	<0.001
Immunoparesis	2.835	0.881–9.129	0.081
Partial immunoparesis	3.014	1.459–6.228	0.003
CRP ≥5 mg/L	1.287	0.725–2.283	0.389
B2M, ≥3.5 mg/L	1.737	0.813–3.713	0.154
B2M, ≥5.5 mg/L	1.924	1.044–3.545	0.036
Albumin, <35 g/L	2/089	0.978–4.465	0.057
Hemoglobin, <90 g/L	2.281	1.206–4.314	0.011
Neutrophil, $<1\times10^9$/L	1.532	0.811–2.897	0.189
Lymphocyte, $<1\times10^9$/L	0.896	0.322–2.495	0.834
eGFR, <60 mL/min/1.73 m^2	2.054	1.163–3.626	0.013
Elevated LDH	2.159	1.183–3.937	0.012
High risk FISH, yes	1.498	0.645–3.477	0.347
ISS stage III	1.924	1.044–3.545	0.036
R-ISS stage III	1.595	0.766–3.321	0.213
High risk defined by Dumontet *et al.* (10)	2.970	1.513–5.829	0.002

OR, odds ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; NT-proBNP, N-aimo terminal fragment of the B-type brain natriuretic peptide; CRP, C-reactive protein; B2M, beta-2-microglobulin; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; FISH, fuorescence in situ hybridization; ISS, international staging system; R-ISS, revised ISS.

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