Infection-related morbidity in a large study of transplant non-eligible newly diagnosed myeloma patients treated with UK standard of care

Infections cause significant morbidity and mortality in myeloma, contributing to up to 50% of early deaths.[1] The increased risk is attributed to immunoparesis and immunosuppressive therapy.[2] The nature and patterns of infections evolved over time, owing to a changing treatment paradigm, which employs a range of systemic therapies from distinct pharmacological classes, all of which confer differing infection risks, and are used in doublet to quadruplet combinations. The aim of first line therapy in transplant non-eligible (TNE) newly diagnosed myeloma (NDMM) patients is to achieve an optimal disease control whilst maintaining a good quality of life (QoL).[3] As such, the burden of infections can negatively impact QoL, whilst treatment interruptions or discontinuations can lead to a sub-optimal haematological response.[4]

We performed a retrospective study of 200 consecutive TNE NDMM patients treated with UK standard of care (2009-2018) to assess infection morbidity and mortality over a 12-month period from diagnosis, and to identify clinical predictors of infective episodes, particularly in elderly co-morbid patients who are largely under-represented in myeloma clinical trials.

Data were collected on baseline characteristics of patients and the disease, in addition to treatment. A number of infection outcomes were collected for each patient over a period of 12 months. A detailed method is described in the *Online Supplementary Materials and Methods*.

The median age of the total cohort was 75 years (range: 40-94), of whom 54% had immunoglobulin G (IgG) subtype, and 44% had International Staging System (ISS) 3 staging. According to the Charlson Comorbidity Index (CCI), 76% of patients were moderately to severely comorbid (CCI: 3-4: 48% and CCI: ≥5 =28%). As such, only 5% of patients were enrolled in a clinical trial. Baseline characteristics of the total cohort are fully presented in the *Online Supplementary Table S1*.

Patients received a median of six cycles of therapy (range: 1-39): IMiD-based (69%), PI: proteasome inhibitor-based (20%) and chemo-based (11%). Median follow up was 67.7 months. Median overall survival (OS)

Table 1. Patient, disease and treatment characteristics of subgroups (infection *vs.* no infection).

Characteristic	Total MM cohort N=200		
	Cohort without infections, n=134	Cohort with infections, n=66	
		All grades n=66	≥ grade 3 n=44
Patient			
Age			
Median (range)	75 (44-94)	76 (40-93)	75 (40-87)
<75	50.7%	48.5%	52.3%
≥75	49.3%	51.5%	47.7%
Charlson comorbidity index (CCI)*			
0-2	20.1%	21.2%	22.7%
3-4	48.5%	46.9%	47.7%
≥5	26.1%	31.8%	29.6%
MM renal impairment (Cr≥140 umol/L)*			
Y	26.9%	18.2%	13.6%
N	70.1%	81.8%	86.4%
Diabetes*			
Y	8.2%	16.7%	20.5%
N	88.8%	83.3%	79.5%
COPD*			
Y	0.7%	15.2%	18.2%
N	96.3%	84.8%	81.8%
Smoking*			
Y or ex	4.5%	22.7%	25%
N	29.1%	27.3%	18.2%
Disease			
ISS staging*			
<3	39.6%	45.5%	43.2%
3	42.5%	46.9%	47.7%
Immunoparesis*			
Y	83.6%	89.4%	57.6%
N	13.4%	10.6%	13.6%
Elevated LDH*			
Y	7.5%	25.8%	27.3%
N	48.5%	46.9%	45.4%

Neutropenia*			
Y	11.9%	16.7%	11.4%
N	84.3%	83.3%	88.6%
Lymphopenia*			
Y	24.6%	31.8%	31.8%
N	72.4%	68.2%	68.2%
Anemia*			
Y	71.6%	80.3%	84.1%
N	24.6%	19.7%	15.9%
Hypercalcemia*			
Y	14.9%	10.6%	13.6%
N	81.3%	87.9%	84.1%
Treatment			
1st line Regimen			
CTDa	29.1%	39.4%	36.4%
CTD	23.1%	19.7%	22.7%
TD	3%	0%	0%
MT	0.7%	0%	0%
MPT	7.5%	4.5%	4.5%
Rd	4.5%	3%	4.5%
RCD	0%	1.5%	2.3%
VD	14.9%	9.1%	4.5%
VCD	3.7%	10.6%	9.1%
VTD	0.7%	0%	0%
CarMelPred	0%	1.5%	2.3%
CD	0.7%	1.5%	2.3%
MP	11.9%	9.1%	11.4%
Combination			
Doublet	35.1%	24.2%	25%
Triplet	64.9%	75.8%	75%
Dose attenuation*			
Y	45.5%	53%	52.3%
N	52.2%	47%	47.7%
Cumulative dexamethasone dose*			
<800 mg	53.7%	53%	61.4%
≥800 mg	43.3%	47%	28.6 %
Antiviral prophylaxis*			
Y	88%	93.9%	93.2%
N	9%	4.5%	4.5%
PCP prophylaxis*			
Y	44.8%	45.5%	47.7%
N	52.2%	53%	50%
Antifungal prophylaxis*			
Y	40.3%	50%	56.8%
N	56.7%	48.5%	40.9%
Pneumococcal vaccine (last 5 years)*			
N	8.2%	19.7%	9.1%
Y	6.7%	3%	0%
Influenza vaccine (last year)*			
N	0%	0%	0%
Y	14.9%	22.7%	9.1%

MM: multiple myeloma, ISS: International Staging System; LDH: lactate dehydrogenase; PCP: pneumocystis pneumonia; COPD: chronic obstructive pulmonary disease. *Number of patients with unknown data of the total cohort: 7 (for CCI), 4 (for renal impairment), 4 (for diabetes), 4 (for COPD), 122 (for smoking status), 29 (for ISS), 4 (for immunoparesis), 77 (for LDH), 5 (for neutropenia), 4 (for lymphopenia), 5 (for anaemia), 6 (for hypercalcaemia), 3 (for dose attenuation), 4 for cumulative dexamethasone dose, 5 (for antiviral prophylaxis), 5 (for PCP prophylaxis), 5 (for antifungal prophylaxis), 165 (for pneumococcal vaccine), 165 (for influenza vaccine). First line therapy consisted: cyclophosphamide with thalidomide and dexamethasone (CTD), attenuated CTD (CTDa), thalidomide with dexamethasone (TD), thalidomide with melphalan (MT), melphalan with prednisolone and thalidomide (MPT), lenalidomide with dexamethasone (Rd), lenalidomide with cyclophosphamide and dexamethasone (RCD), bortezomib and dexamethasone (VD), bortezomib with cyclophosphamide and dexamethasone (VCD), bortezomib with thalidomide and dexamethasone (VCD), carfilzomib with melphalan and prednisolone (CarMePred), cyclophosphamide with dexamethasone (CP), and melphalan with prednisolone (MP).

and progression free survival (PFS) were 33.5 and 9.2 months, respectively. The reasons for these modest survival outcomes are multifactorial: advanced age, comorbidities, dose attenuation in 48% of patients, and early discontinuation due to toxicities, in addition to largely thalidomide-based treatment (CTD/CTDa), or use of doublet over triplet bortezomib combinations. Baseline characteristics of (infection *vs.* no-infection) subgroups are presented in Table 1.

There were 116 documented infections, of which 72 were ≥grade 3 (≥g3). Two-thirds of infections occurred in the first 6 months. Thirty two episodes were diagnosed

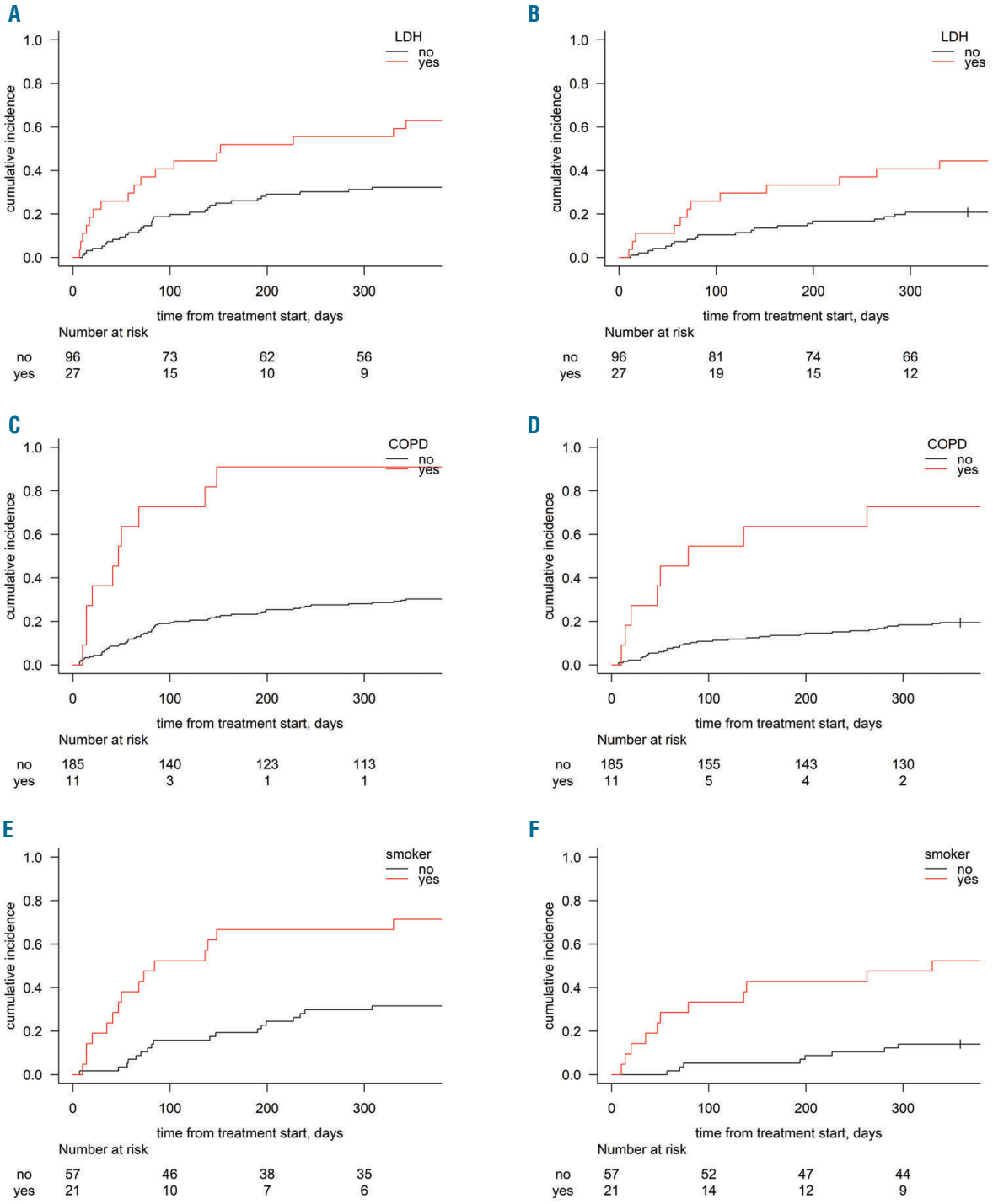


Figure 1. Cumulative incidence curves of infections. (A) Cumulative incidence curves of all infections according to elevated lactate dehydrogenase (LDH) (Y *vs.* N): (63% *vs.* 32.3%, *P*=0.00046). (B) Cumulative incidence curves of ≥g3 infections according to elevated LDH (Y *vs.* N): (44.4% *vs.* 20.8%, *P*=0.00743). (C) Cumulative incidence curves of all infections according to chronic obstructive pulmonary disease (COPD) (Y *vs.* N): (90.9% *vs.* 30.3%, *P*=1.71x10^{-8}). (D) Cumulative incidence curves of ≥g3 infections according to COPD (Y *vs.* N): (72.7% *vs.* 19.5%, *P*=1.79x10-5). (E) Cumulative incidence curves of all infections according to smoking (Y *vs.* N): (71.4% *vs.* 31.6%, *P*=7.32 x10^{-5}). (F) Cumulative incidence curves of ≥g3 infections according to smoking (Y *vs.* N): (52.4% *vs.* 14%, *P*=0.000613).

with micro-guidance (*Online Supplementary Table S2*), whilst 84 were clinically diagnosed. Median time to first episode was 70 days (interquartile range [IQR]: 33-147 days) for all grade infections and 72 days (IQR: 36-197) for ≥g3.

Cumulative incidence of first infections over 12 months in the total cohort for all infections and ≥g3 infections were 33% and 22%, respectively, *Online Supplementray Figure 1SA-B*. The median number of all infections and ≥g3 infections per patient were: 1 (range: 1-7) and 1 (range: 1-5), respectively. Twenty eight patients experienced more than one infection over the 12 month period (median 2, range: 2-7). Episodes occurred during induction (49.1%), remission (17.2%), and progressive disease (PD) (13.8%) and during second line therapy (19.8%). Thirty seven episodes occurred in winter seasonal period (December to March), *Online Supplementary Table S3*. Among 184 patients, the occurrence of at least one infection in the first 100 days led to higher odds of another infection beyond 100 days, but this was not significant (P=0.4).

Most common infection sites were respiratory tract (n=61), and genitourinary tract (n=22), *Online Supplementary Table S4*. Fifty six episodes required a significant inpatient stay (>3 days), of which two required ICU admissions. At 3, 6 and 12 months, the cumulative incidence of infection-related deaths were: 1%, 2% and 4%, and of deaths from other causes were: 6%, 10% and 18%.

Sixteen deaths occurred within the first 100 days: infections (2: sepsis and lower respiratory tract infection [LRTI]), PD (4), myocardial infarction (MI) (1), acute kidney injury (AKI) (2), and unascertained cause (7). Causes of the eight infection-related deaths at 12 months were: sepsis (1), LRTI (4), infectious chronic obstructive pulmonary disease (COPD) exacerbation (1), peripherally inserted central catheter (PICC) line associated infection (1) and infection of unknown origin (1).The 36 deaths at 12 months from other causes were: PD (7), MI (2), respiratory insufficiency (2), AKI (1), bowel obstruction (1), and unascertained cause (23).

In the univariate analysis (UVA) of cumulative incidence of all grade and ≥g3 infections, elevated lactate dehydrogenase (LDH), COPD, and smoking were associated with significantly higher infection incidence (Figure 1A-F). Patients aged ≥75 years, those with concurrent diabetes, significant comorbidity (CCI≥5), or treatment with a triplet combination, all experienced a trend towards a higher incidence, *Online Supplementary Table S5*. Baseline LDH and COPD remained as independent factors in multivariate (MVA) competing risks regression for all-grade infections.

By MVA Poisson regression, elevated baseline LDH and smoking predicted for higher infection rate, whilst administering a high number of cycles of therapy (≥6 *vs.* <6) was associated with reduced infection rate, *Online Supplementary Table S6*.

The same analysis for ≥g3 infections within 12 months also demonstrated that elevated LDH and smoking predicted for a higher risk of infections, whilst administering a high number of cycles of therapy and achieving a deep response (≥ very good partial response [VGPR] *vs.* ≤ partial response [PR]) appeared to have a protective effect, *Online Supplementary Table S7*.

Elevated LDH and smoking predicted for higher risk of prolonged infection-related hospitalisation (>3 days), while favourable response appeared protective, *Online Supplementary Table S8*.

Pneumocystis carinii pneumonia (PCP) prophylaxis (only received by 45% of patients) did not result in a significant reduction in the cumulative incidence of infections, and was not an independent factor by UVA and MVA.

The 6-month landmark analysis demonstrated that median OS among 6-month survivors was lower in the subgroup of patients who experienced infections in the first 6 months compared to those who did not, for all grade (P=0.0838) and ≥g3 infections (P=0.0176), (Figures 2A-B). This effect was also evident when occurrence of first infection was tested as time-dependent variable in the presence of other prognostic factors for OS and PFS, *Online Supplementary Table S9*.

Causes of death after the first 6 months included PD (36), LRTI (20), sepsis (6), AKI (3), SPM (second primary malignancy) (2), COPD (1), congestive cardiac failure (CCF) (1), pulmonary edema (1), Creudzfeld-Jakob disease (1), and unascertained cause (33).

Managing infective complications of novel therapies has become more important in recent years as survival of myeloma patients continues to improve. In this study, the cumulative incidence of all grade infections is consistent with a combined analysis of 476 patients from two NDMM trials (33% *vs.* 33.2%).[5] However, our cohort experienced a higher incidence of ≥g3 infections (22% *vs.* 11%).

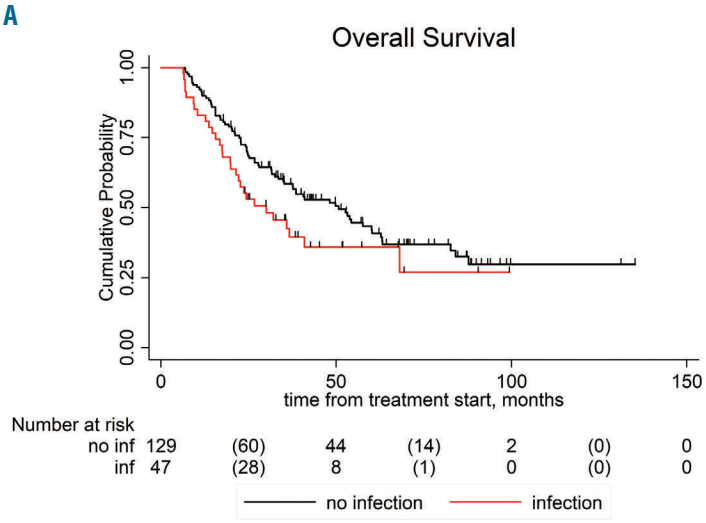
Baseline LDH is a prognostic indicator of myeloma disease activity.[6] Our study is consistent with analysis of the FIRST trial in TNE NDMM, where a validated prediction model retained elevated LDH in the definition of high risk from treatment-related ≥g3 infections.[7] Our results are also consistent with an Australian study of 199 patients which did not find an independent association between the choice of therapy (Immunomodulatory imide drugs [IMiD] *vs.* proteasome inhibitor) and infections.[8]

The overwhelming effect of COPD and smoking on infection outcomes explains the incidence of respiratory tract infections in our cohort. This may explain why we could not detect the effect of other "suspect" variables such as diabetes, immunoparesis, renal disease, and CCI on infection risk, some of which were significant in OS and PFS analyses. Effect of influenza and pneumococcal immunisations could not be adequately explored due to the high number of patients with an unknown vaccination status. However, patients who received immunisation showed a lower cumulative incidence of infections compared to those who did not or those with unknown status, see *Online Supplementary Results.*

We attempted to explore the effect of infection occurrence on disease control and outcomes. Delivery of fewer cycles of first line treatment and suboptimal hematological response (≤PR) were associated with a higher infection risk. First infectious episode was associated with worse PFS and OS when tested as time-dependent covariates in MVA PFS and OS models. However, best response (≥VGPR *vs.* ≤PR) as a binary outcome was not found to be associated with infection within the first 12 months, by logistic regression among 12-month survivors.

These findings could be explained by the hypothesis that infections lead to less intensive treatment (dose reductions, delays and interruptions) thus compromising disease control. On the other hand, poor response to treatment or early progression/relapse could in theory increase infection risk because of disease and therapy-related immunosuppression.

In view of the recent shift in the UK towards continuous upfront lenalidomide based on FIRST trial data,[9] in addition to recent EMA approval of continuous quadru-



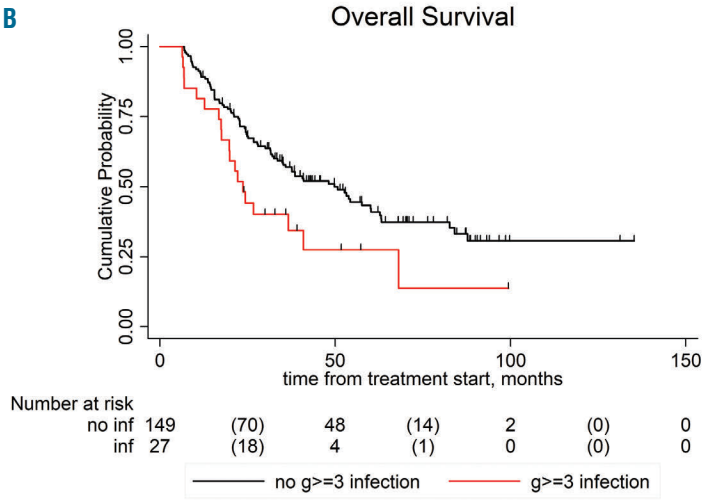


Figure 2. Landmark overall survival analysis. (A) Landmark overall survival (OS) analysis according to (no infections *vs.* all infections): (44.7 *vs.* 23 months, *P*=0.0838). (B) Landmark OS analysis according to (no ≥g3 infections *vs.* ≥g3 infections): (43.8 *vs.* 17.7 months, *P*=0.0176).

plet therapy D-VMP,[10] close monitoring and tolerable dosing are imperative to limit infection complications. The TEAMM trial demonstrated that the prophylactic use of 12 weeks of levofloxacin for myeloma patients receiving therapy, significantly reduced febrile episodes and deaths without increasing healthcare-associated infections.[11]

We recommend that patients with elevated LDH who may require more intensive therapy, in addition to those presenting with extensive myeloma related end-organ disease, or significant co-morbidities, or with COPD, should be more closely monitored for treatment toxicity and offered education about recognition of early signs of infections. They should receive standard antifungal and antiviral prophylaxis and should be advised to update their immunisation schedules. Primary antibacterial prophylaxis, as demonstrated by TEAMM trial,[11] should be considered in these patients, or in those with a history of recurrent respiratory tract infections. Intravenous immunoglobulin should be considered in selected cases for those with severe immunoparesis unresolved following first line myeloma therapy.

Our study is limited by its retrospective nature, possibility of under-reported infection episodes, incomplete cause of death data, and use of thalidomide or bortezomib-based therapy, which are not reflective of the recent changes in the myeloma treatment paradigm towards continuous therapy.

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References

1. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. J

Clin Oncology. 2005;23(36):9219-9226.
2. Teh BW, Harrison SJ, Pellegrini M, Thursky KA, Worth LJ, Slavin, M.A. Changing treatment paradigms for patients with plasma cell myeloma: impact upon immune determinants of infection. Blood Rev. 2014;28(2):75-86.
3. Mateos MV, San Miguel JF. Management of multiple myeloma in the newly diagnosed patient. Hematology Am Soc Hematol Educ Program. 2017;(1):498-507.
4. Zweegman S, Palumbo A, Bringhen S, Sonneveld P. Age and aging in blood disorders: multiple myeloma. Haematologica. 2014; 99(7):1133-1137.
5. Offidani M, Corvatta L, Bringhen L, et al. Infection complications in 476 patients with newly diagnosed multiple myeloma treated with lenalidomide or bortezomib combinations. Blood. 2015;126(23): 5365.
6. Simonsson B, Brenning G, Källander C, Ahre A. Prognostic value of serum lactic dehydrogenase (S-LDH) in multiple myeloma. Eur J Clin Invest. 1987;17(4):336-339.
7. Dumontet C, Hulin C, Dimopoulos MA, et al. A predictive model for risk of early grade≥3 infection in patients with multiple myeloma not eligible for transplant: analysis of the FIRST trial. Leukemia. 2018;32(6):1404-1413.
8. Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA. Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy. Br J Haematol. 2015;171(1):100-108.
9. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-917.
10. Mateos MV, Dimopoulos MA, Cavo M, el al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378(6):518-528.
11. Drayson MT, Bowcock S, Planche T, el al. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Oncol. 2019;20(12):1760-1772.