Early mortality in multiple myeloma: Experiences from a single institution

Yeh-Ku Chen†, Shao-Min Han†, Youngsen Yang†, Tseng-Hsi Lin1,2†, Huey-En Tzeng†, Kuang-Hsi Chang5, Wen-Li Hwang1, Chieh-Lin Jerry Teng1,4,6

Division of Hematology/Medical Oncology, Department of Medicine, Taichung Veterans General Hospital, Taiwan, School of Medicine, College of Medicine, China Medical University, Taiwan, Division of Transfusion Medicine, Department of Pathology and Laboratory Medicine, Taichung Veterans General Hospital, Taiwan, Department of Medicine, Chung Shan Medical University, Taiwan, Department of Medical Research and Education, Taichung Veterans General Hospital, Taiwan, Department of Life Science, Tunghai University, Taiwan

Objective: Multiple myeloma (MM) is a hematological malignancy that presents with infection, anemia, bone lesions, renal function impairment, and hypercalcemia. The survival of MM patients has improved in recent decades; however, early mortality remains a critical problem. The aim of this study was to identify the etiologies and clinical variables associated with early mortality in MM. In addition, the effects of bortezomib on reducing early mortality incidence were investigated.

Method and materials: Medical records from 122 MM patients diagnosed between November 2007 and December 2013 were retrospectively reviewed. Early mortality was defined as death by any cause within the first 180 days after pathological diagnosis.

Results: In newly diagnosed MM patients, early mortality occurred in 22.95% of patients. Infection accounted for 67.86% of early deaths. Multivariate analyses by Cox proportional-hazards regression showed that higher β2-microglobulin (P < 0.001) and serum lactate dehydrogenase (P < 0.001) levels, and lower serum albumin levels (P < 0.001) were associated with early mortality. Both first-line and greater than or equal to second-line bortezomib treatments were not associated with superior 180-day overall survival (P = 0.546 for first-line bortezomib treatment; P = 0.066 for greater than or equal to second-line bortezomib treatment).

Conclusion: Our results suggest that infection is the leading cause of early death in MM. High β2-microglobulin, high serum lactate dehydrogenase, and low serum albumin levels are poor prognostic factors for early mortality. Bortezomib therapy does not appear to reduce the incidence of early mortality in MM patients.

Keywords: Multiple myeloma, Mortality, Bortezomib

Introduction
Multiple myeloma (MM) accounts for approximately 10% of all hematological malignancies. Its incidence is increasing, with the median age at diagnosis currently being 70 years. The pathophysiology of MM involves deregulated clonal plasma cell proliferation in the bone marrow and deposition of monoclonal plasma cells in the target organs. Typical clinical manifestations include infection, anemia, bone lesions, renal function impairment, and hypercalcemia. Although MM remains an incurable disease, the clinical outcomes have improved significantly in the last few decades. It is believed that high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation and the introduction of novel therapies to produce a greater treatment response have played critical roles in the improvements in survival.

However, although the overall survival time of MM has improved, early mortality remains problematic. Prior to the introduction of novel therapeutic agents, death occurred within 60 days of diagnosis in 10% of newly diagnosed MM patients, with infection being the leading cause. Even in the current era of novel therapies, Kumar et al. showed that the 1-year mortality rate in MM remains as high as 13%. This result suggests the possibility that risk-adapted therapy may be a solution for early mortality in MM.
Cytogenetics using fluorescent in situ hybridization (FISH) has been experimentally incorporated into risk stratification-based therapy for MM. However, FISH is not routinely performed for MM cytogenetics at every institution, with the complex technical requirements and high costs being major issues associated with this method. Moreover, not all novel agents have been approved or are reimbursed in every country. To further understand what causes patients to be at high risk of early mortality, we performed a retrospective study on MM patients from our institution.

The aim of this study was to identify the etiologies of early mortality in MM and the clinical variables that could be used to predict early death. Because bortezomib is considered to be effective for the treatment of both newly diagnosed and relapsed/refractory MM patients and has been widely used in Taiwan for relapsed/refractory and newly diagnosed MM since March 2010 and October 2011, respectively, this study also examined whether bortezomib treatment could reduce the risk of early mortality in MM patients.

Patients and methods

Patients

Newly diagnosed myeloma patients were enrolled in the study. Patients younger than 20 years of age, who were not followed-up regularly, and who were positive for human immunodeficiency virus infection were excluded. The medical charts for 122 myeloma patients diagnosed between November 2007 and December 2013 were reviewed. This retrospective study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan. In accordance with the regulations of the Institutional Review Board, signed informed consent was not required and, thus, not obtained.

Definitions and patient stratification

Early mortality was defined as death by any cause within the first 180 days following pathological diagnosis. To identify possible poor prognostic factors for early death, clinical characteristics were compared between patients with \( n = 28 \) and without \( n = 94 \) early mortality. As some patients died very quickly after the diagnosis and did not have enough time to respond to the anti-myeloma treatments, only patients with a survival time of more than 30 days \( n = 107 \) were analyzed to determine whether bortezomib decreased the incidence of early death. These patients were stratified into the non-bortezomib treatment group \( n = 25 \), the first-line bortezomib treatment group \( n = 48 \), and the greater than or equal to second-line bortezomib treatment group \( n = 34 \) according to the different reimbursement criteria in the different time periods.

Statistical analysis

Patients’ clinical parameters were compared using the Mann–Whitney U test, chi-square tests, or analysis of variance as appropriate. Cox proportional-hazards regression was performed to evaluate risk factors for early mortality by both univariate and multivariate analyses and to study whether bortezomib decreased the incidence of early death. All results are presented as the mean ± standard error of the mean and were considered to be significant at \( P < 0.05 \). All statistical analyses were performed using SPSS software, version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the study cohort

The characteristics of the study cohort are shown in Table 1. Briefly, the median age of the study cohort \( n = 122 \) was 66.02 years (range: 23–95 years). Male patients accounted for 55.74% of the cohort. Using the Durie–Salmon staging system, 34.43, 26.23, and 39.34% of the study patients were diagnosed with stages I, II, and III MM, respectively. Using the International Staging System, 13.93, 40.98, and 45.09% of the patients were diagnosed with stages I, II, and III MM, respectively. In terms of the first-line treatment, 42.26% of patients were treated by bortezomib-based regimens and 54.10% of patients received non-bortezomib-based regimens.

Incidence and cause of early mortality in newly diagnosed MM patients

Early mortality occurred in 28 of the 122 (22.95%) newly diagnosed MM patients. Of the 28 patients with early mortality, 15 (53.57%) died within the first 30 days after the diagnosis. The cause of death and clinical characteristics of these 28 patients are shown in Table 2. Infection was the leading cause of death, accounting for 67.86% (19/28) of cases. Of the patients who died of infection, pneumonia was the most common cause of infection-related death, and was observed in 14 of 19 patients (73.68%). The causative pathogens were identified in 79% (15/19) of patients who died of infection; however, the identified pathogens were heterogeneous.

Clinical variables associated with early mortality in newly diagnosed MM patients

To identify the possible risk factors for early mortality in newly diagnosed MM patients, clinical variables were compared between patients with an overall survival time of less than 180 days \( n = 28 \) and more than 180 days \( n = 94 \) (Table 1). Briefly, patients with a survival time of less than 180 days had higher serum lactate dehydrogenase levels \( (P < 0.001) \), total serum protein levels \( (P = 0.029) \), and serum creatinine levels \( (P = 0.027) \) than patients who survived for more than 180 days.
days. However, the serum albumin levels were lower in patients who died within the first 180 days than in those who survived for more than 180 days ($P < 0.001$).

Hazard ratios (HRs) were calculated using univariate and multivariate analyses to validate the associations of clinical variables with early mortality (Table 3). By univariate analyses, higher β2-microglobulin ($P = 0.001$), total serum protein ($P = 0.010$), and serum lactate dehydrogenase levels ($P < 0.001$), and lower serum albumin levels ($P < 0.001$) were found to be associated with early mortality. In contrast, patient age, sex, disease stage, and serum calcium, serum creatinine, and hemoglobin levels were not significantly associated with early mortality. To further consolidate the data from the univariate analyses, multivariate analysis was performed after adjustment for β2-microglobulin, serum lactate dehydrogenase, serum albumin, and total serum protein levels. The results showed that higher β2-microglobulin levels ($P < 0.001$) and serum lactate dehydrogenase levels ($P < 0.001$), and lower serum albumin levels ($P < 0.031$), but not total protein ($P = 0.243$), were significantly and independently associated with early mortality.

**Bortezomib was not associated with superior 180-day, 1-year, and 2-year overall survivals**

Following identification of risk factors for early mortality in MM patients, the ability of bortezomib to lower the incidence of early mortality was investigated. The clinical characteristics of patients in the non-bortezomib, first-line bortezomib, and greater than or equal to second-line bortezomib treatment groups were compared (Table 4). The majority of clinical variables did not differ significantly between the three groups of patients, except for the mean follow-up time ($P = 0.008$) and subtypes of myeloma ($P = 0.011$).

To explore whether bortezomib could reduce early mortality and provide survival benefits to MM patients, the HRs for the different treatments for the 180-day, 1-year, and 2-year overall survivals were analyzed (Table 5). Only patients with an overall survival time more than 30 days (Table 5) were analyzed to exclude patients not having enough time to respond to the anti-myeloma treatments. With no bortezomib as the comparison treatment, the results showed that neither first-line bortezomib (HR: 0.70; 95% confidence interval [CI]: 0.22–2.21; $P = 0.546$) nor greater than or equal to second-line bortezomib...
treatment (HR: 0.13; 95% CI: 0.02–1.15; \( P = 0.066 \)) was associated with a superior 180-day overall survival rate. In addition, neither first-line nor greater than or equal to second-line bortezomib treatment was associated with superior 1-year (HR: 0.79; 95% CI: 0.33–1.91; \( P = 0.599 \) for first-line bortezomib treatment; HR: 0.31; 95% CI: 0.09–1.04; \( P = 0.058 \) for greater than or equal to second-line bortezomib treatment) or 2-year survival rates (HR: 0.89; 95% CI: 0.45–1.74; \( P = 0.731 \) and HR: 0.48; 95% CI: 0.21–1.07; \( P = 0.074 \), respectively).

### Discussion

In the current study, we showed an early mortality rate of 22.95% in newly diagnosed MM patients, which is higher than what has been observed previously. In addition, we found that infection was the major cause of death in our cohort (67.86%). Specifically, pneumonia was the most common cause of infection-related death (73.68%). The high infection rate observed in this study raises the question as to whether prophylactic antibiotic treatment, which is

### Table 2 Causes of early mortality in MM patients

| Pt No. | Age (years) | Sex | Cause of death (infection type, if available) | Pathogen (culture specimen) | Survival time (days) | ISS | DSS |
|--------|-------------|-----|-----------------------------------------------|----------------------------|----------------------|-----|-----|
| 1      | 86          | M   | Infection (pneumonia)                         | Escherichia coli (B/C)     | 0                    | III | IA  |
| 2      | 51          | M   | Infection (pneumonia)                         | Klebsiella pneumoniae (B/C)| 0                    | III | IIIB|
| 3      | 63          | F   | Pulmonary embolism                             |                            |                      |     |     |
| 4      | 77          | F   | Acute renal failure                            |                            |                      |     |     |
| 5      | 73          | M   | Infection (septic shock)                       | E. coli (B/C)              | 5                    | III | IIA |
| 6      | 48          | M   | Cardiac arrest                                 |                            | 8                    | II  | IA  |
| 7      | 79          | M   | Infection (septic shock)                       | Enterococcus faecium (B/C)| 9                    | III | IIIB|
| 8      | 45          | M   | Infection (pneumonia)                          | OSSA (S/C)                 | 10                   | II  | IB  |
| 9      | 68          | M   | Infection (pneumonia)                          | CRAB (S/C)                 | 11                   | III | IIB |
| 10     | 77          | M   | Infection (pneumonia)                          | Viridans streptococci (throat swab) | 17                  | IIIB|
| 11     | 72          | M   | Intracranial hemorrhage                        |                            |                      |     | IIB |
| 12     | 75          | M   | Infection (pneumonia)                          | Pseudomonas aeruginosa (B/C)| 21                  | IIB |
| 13     | 56          | M   | Cardiac arrest                                 |                            | 22                   | III | IIA |
| 14     | 64          | F   | Infection (pneumonia)                          | K. pneumoniae (B/C)        | 23                   | II  | A   |
| 15     | 70          | F   | Acute renal failure                            |                            | 27                   | II  | IIA |
| 16     | 47          | M   | Infection (pneumonia)                          | MRSA (B/C)                 | 36                   | II  | IIB |
| 17     | 64          | M   | Infection (pneumonia)                          | Not identified             | 47                   | IIIB|
| 18     | 66          | F   | Infection (pneumonia)                          | Enterobacter cloacae (B/C)| 47                   | II  | IA  |
| 19     | 47          | M   | Infection (pneumonia)                          | Not identified             | 48                   | II  | IA  |
| 20     | 82          | M   | Infection (pneumonia)                          | K. pneumoniae (B/C)        | 96                   | III | IIB |
| 21     | 62          | M   | Infection (septic shock)                       | OSSA (B/C)                 | 108                  | III | IIB |
| 22     | 29          | M   | Infection (pneumonia)                          | Not identified             | 116                  | I   | IA  |
| 23     | 75          | M   | Infection (urosepsis)                          | P. aeruginosa (U/C)        | 132                  | III | IA  |
| 24     | 53          | F   | Unknown                                       |                            | 138                  | I   | IA  |
| 25     | 80          | F   | Hepatic failure                                |                            | 144                  | II  | IA  |
| 26     | 77          | M   | Infection (pneumonia)                          | E. coli (S/C)              | 147                  | III | IIA |
| 27     | 64          | F   | Infection (pneumonia)                          | Not identified             | 157                  | II  | IA  |
| 28     | 58          | M   | Unknown                                       |                            | 167                  | II  | IA  |

M, male; F, female; ISS, international staging system; DSS, Durie–Salmon staging system; B/C, blood culture; OSSA, oxacillin-resistant Staphylococcus aureus; S/C, sputum culture; CRAB, carbapenem-resistant Acinetobacter baumannii; MRSA, methicillin-resistant S. aureus.

### Table 3 HR for early mortality in 122 MM patients

| Beta-Microglobulin | Crude HR | 95% CI | \( P \) | Adjusted HR | 95% CI | \( P \) |
|--------------------|----------|--------|---------|-------------|--------|---------|
| 2-Microglobulin    | 1.000    | 1.000  | 1.000   | 1.000       | 1.000  | 1.000   |
| Albumin            | 0.996    | 0.750  | 1.272   | 0.010       | 0.930  | 1.332   |
| Total protein      | 1.217    | 1.049  | 1.412   | 0.010       | 1.113  | 1.332   |
| Lactate dehydrogenase | 1.003  | 1.002  | 1.004   | <0.001      | 1.005  | 1.006   |
| Age                | 0.987    | 0.052  | 0.027   | 0.019       | 0.970  | 1.034   |

**HR,** hazard ratio; CI, confidence interval; ISS, international staging system; DSS, Durie–Salmon staging system.
Table 4 Clinical characteristics of MM patients with mortality between 31 and 180 days following diagnosis

|                          | Non-bortezomib treatment (n = 25) | First-line bortezomib treatment (n = 48) | Greater than or equal to second-line bortezomib treatment (n = 54) | P       |
|--------------------------|-----------------------------------|-----------------------------------------|---------------------------------------------------------------|---------|
| Age (years)              | 67.92 ± 12.04                     | 63.94 ± 12.10                           | 67.18 ± 11.22                                                 | 0.298*  |
| Sex (%)                  |                                   |                                         |                                                               |         |
| Male                     | 16 (64.00%)                       | 22 (45.83%)                             | 20 (58.82%)                                                  | 0.271†  |
| Female                   | 9 (36.00%)                        | 26 (54.17%)                             | 14 (41.18%)                                                  |         |
| β2-Microglobulin (660–2740 ng/dl) | 7089.26 ± 6357.09 | 7814.02 ± 5599.77                       | 8057.91 ± 7982.24                                            | 0.875*  |
| Albumin (3.5–5.0 g/dl)   | 3.23 ± 0.79                       | 3.38 ± 0.65                             | 3.36 ± 0.64                                                  | 0.658*  |
| Total protein (6.0–8.0 g/dl) | 9.34 ± 1.93                     | 9.11 ± 2.67                             | 9.09 ± 2.68                                                  | 0.920*  |
| Lactate dehydrogenase (140–240 IU/l) | 228.68 ± 132.89     | 221.55 ± 108.10                         | 180.06 ± 114.44                                             | 0.191*  |
| Calcium (8.4–10.2 mg/dl)  | 8.44 ± 1.28                       | 8.08 ± 2.00                             | 8.31 ± 1.39                                                  | 0.648*  |
| Creatinine (0.7–1.4 mg/dl) | 2.61 ± 3.02                       | 4.15 ± 12.20                            | 1.95 ± 1.87                                                  | 0.481*  |
| Hemoglobin (12.0–17.5 g/dl) | 9.92 ± 2.24                       | 9.95 ± 2.54                             | 9.71 ± 2.32                                                  | 0.900*  |
| Follow-up time (days)    | 858.32 ± 687.30                   | 694.29 ± 379.66                         | 1080.12 ± 602.02                                            | 0.008*  |
| Disease subtype          |                                   |                                         |                                                               |         |
| IgG                      | 10 (40.00%)                       | 19 (39.58%)                             | 13 (38.24%)                                                  | 0.111†  |
| IgA                      | 4 (16.00%)                        | 10 (20.84%)                             | 10 (29.41%)                                                  |         |
| Light chain disease      | 0 (0.00%)                         | 13 (27.08)                              | 5 (14.71%)                                                   |         |
| Others                   | 11 (44.00%)                       | 6 (12.50%)                              | 6 (17.64%)                                                   |         |
| ISS                      |                                   |                                         |                                                               |         |
| I                        | 3 (12.00%)                        | 9 (18.75%)                              | 5 (14.71%)                                                   | 0.078†  |
| II                       | 16 (64.00%)                       | 14 (29.17%)                             | 14 (41.18%)                                                  |         |
| III                      | 6 (24.00%)                        | 25 (52.08%)                             | 15 (44.11%)                                                  |         |
| DSS                      |                                   |                                         |                                                               |         |
| I                        | 8 (32.00%)                        | 19 (39.58%)                             | 11 (32.35%)                                                  | 0.930†  |
| II                       | 7 (28.00%)                        | 10 (20.84%)                             | 9 (26.47%)                                                   |         |
| III                      | 10 (40.00%)                       | 19 (39.58%)                             | 14 (41.18%)                                                  |         |

Data are presented as mean ± standard error of mean or as number (percentage).
IgG, immunoglobulin G; IgA, immunoglobulin A; ISS, international staging system; DSS, Durie-Salmon staging system.
*Data were compared using analysis of variance.
†Data were compared using the chi-square test.

not part of routine practice at our institution, should be a standard of care in newly diagnosed MM patients. Furthermore, the optimal prophylactic antibiotic and appropriate dosing schedule remain unclear and warrant further investigation.

Previous studies have provided some clues regarding these issues. In the era of chemotherapeutic therapy, administering trimethoprim–sulfamethoxazole for the first 2 months of initial chemotherapy has been shown to be an effective and inexpensive prophylaxis for early bacterial infection in MM patients. Nowadays, novel therapies are delivered to the majority of newly diagnosed MM patients as first-line treatment. A study by Jung et al. showed that bortezomib-containing regimen-treated MM patients who underwent levofloxacin prophylaxis had a lower infection rate than those not on levofloxacin prophylaxis (17.5% vs. 30.9%, P = 0.037). Of note, in our study, the majority of pathogens identified in our patients were sensitive to levofloxacin. Unfortunately, none of these patients had ever received any prophylactic antibiotics. While these findings suggest that antibiotic prophylaxis therapy may have been appropriate for the treatment of our MM patients, it is unknown if prophylactic antibiotic therapy truly reduces early mortality rates or improves overall survival time in MM patients, and further studies are required to address these points.

In addition to prophylactic antibiotics, identifying MM patients at high risk of early mortality is also important. In order to identify possible poor prognostic factors for early mortality in MM, we compared the clinical variables between patients who died within and after 180 days of diagnosis. The identified variables were validated using both univariate and multivariate analyses by Cox proportional-hazards regression. It has been previously reported by Kumar et al. that serum albumin levels <3.5 g/dl, serum...
and by the limited number of patients investigated. Similarly, we observed that lower serum albumin levels ($P < 0.001$) and higher $\beta_2$-microglobulin ($P < 0.001$) and serum lactate dehydrogenase levels ($P < 0.001$) were associated with early mortality in our patient cohort. These results suggest that more attention should be paid to MM patients with these unfavorable prognostic factors.

Diagnostic delay may be another possible explanation for the high early mortality rate in our cohort. Although the age and disease stage were not significantly associated with early mortality in the current study, and a study by Friese et al. showed that delayed treatment, but not delayed diagnosis, was a significant predictor of complications in MM patients, 53.57% (15/28) of early mortality cases observed in our study cohort occurred within the first 30 days following diagnosis. Among all anti-myeloma treatments, bortezomib is considered the drug of choice for rapid myeloma cell reduction. However, a median of 1.4 months is still needed to observe the first response in patients treated with bortezomib plus melphalan and prednisolone. These data suggest that the patients who died in the first 30 days might not have had enough time to respond to the anti-myeloma treatments. Additionally, more than 80% of patients included in this study were diagnosed to have stage II or III disease, which may also be associated with the high observed incidence of early mortality.

Surprisingly, both first-line and Greater than or equal to second-line bortezomib treatments did not decrease early mortality in MM patients in our study. This result may be partially due to the majority of early mortality cases observed in this study occurring within the first 30 days following diagnosis. However, even after excluding these patients, no reduction in early mortality by bortezomib treatment was observed. Furthermore, neither first-line nor Greater than or equal to second-line bortezomib treatment was associated with superior 1-year and 2-year overall survivals, which differed from the results of multiple previous phase III trials. Limitations related to the extent of bortezomib dosage that is reimbursed by the Taiwan national health insurance and the lack of effective bortezomib or lenalidomide maintenance therapy may be possible explanations for these differing results. Unfortunately, these clinical obstacles translate into poor treatment outcomes in MM patients in Taiwan. In fact, Huang et al. previously reported that the median overall survival time for transplant-ineligible MM patients in Taiwan was only 22.0 months, which is less than what has been reported previously.

This study is limited by its retrospective study design and by the limited number of patients investigated. Because of the retrospective nature, the bortezomib-containing regimens and treatment schedules delivered to MM patients in the current study were relatively heterogeneous. In addition, the impact of autologous hematopoietic stem cell transplantation ($n = 5$) and lenalidomide ($n = 16$) was not considered in the current study because only a few patients had received these therapies.

In conclusion, our study showed that early mortality occurred in more than 20% of newly diagnosed MM patients and that infection was the leading cause of death in these patients. Higher lactate dehydrogenase levels, higher $\beta_2$-microglobulin levels, and lower albumin levels were predictors of early mortality. Bortezomib does not appear to reduce the incidence of early mortality in MM patients, largely owing to diagnostic delay. Appropriate antibiotic prophylaxis therapy should be considered in MM patients, especially those at high risk of early mortality. However, prospective and randomized control studies are required to validate the conclusions of this study.

Disclaimer statements
Contributors Y.-K.C. analyzed the data and wrote the manuscript. S.-M.H. analyzed the data and designed the study. Y.Y. took care of the patients and designed the study. T.-H.L. took care of the patients and designed the study. H.-E.T. took care of the patients and designed the study. K.-H.C. analyzed the data. W.-L.H. designed the study. C.-L.J.T. designed the study, wrote the manuscript, and analyzed the data.

Funding None.

Conflicts of interest C.-L.J.T. received a speaking fee from Janssen Pharmaceuticals for presenting data from this study. The other authors have no conflicts of interest to declare.

Ethics approval This study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan.

References
1 Kyle RA, Rajkumar SV. Multiple myeloma. Blood. 2008;111: 2962–72.
2 Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516–20.
3 Attal M, Harousseau JL, Facon T, Guillot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. New Engl J Med. 2003;349: 2495–502.
4 Mateos MV, San Miguel JF. How should we treat newly diagnosed multiple myeloma patients? Hematology Am Soc Hematol Educ Program. 2013:2013:488–95.
5 Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, 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 Oncol. 2005;23:9219–26.
6 Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122–8.

7 Kumar SK, Michael JR, Buadi FK, Dingli D, Dispenzieri A, Fonseca R, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc. 2009;84:1095–110.

8 Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28:2259–66.

9 Palumbo A, Ambrosini MT, Benevolo G, Pregno P, Pescosta N, Callea V, et al. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. Blood. 2007;109:2767–72.

10 Oken MM, Pomeroy C, Weisdorf D, Bennett JM. Prophylactic antibiotics for the prevention of early infection in multiple myeloma. Am J Med. 1996;100:624–8.

11 Jung SH, Kang SJ, Jang HC, Ahn JS, Yang DH, Lee SS, et al. Effect of levofloxacin prophylaxis for prevention of severe infections in multiple myeloma patients receiving bortezomib-containing regimens. Int J Hematol. 2014;100:473–7.

12 Friese CR, Abel GA, Magazu LS, Neville BA, Richardson LC, Earle CC. Diagnostic delay and complications for older adults with multiple myeloma. Leuk Lymphoma. 2009;50:392–400.

13 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropp M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. New Engl J Med. 2008;359:906–17.

14 Mateos MV, Bringhen S, Richardson PG, Lahuerta JJ, Larocca A, Oriol A, et al. Bortezomib cumulative dose, efficacy, and tolerability with three different bortezomib–melphalan–prednisone regimens in previously untreated myeloma patients ineligible for high-dose therapy. Haematologica. 2014;99:1114–22.

15 Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib–melphalan–prednisone–thalidomide followed by maintenance with bortezomib–thalidomide compared with bortezomib–melphalan–prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol. 2010;28:5101–9.

16 Dimopoulos MA, Delforge M, Hajek R, Kropp M, Petrucci MT, Lewis P, et al. Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomized phase III trial. Haematologica. 2013;98:784–8.

17 Huang TC, Chen JH, Wu YY, Chang PY, Dai MS, Chao TY, et al. The treatment outcome of multiple myeloma patients ineligible for hematopoietic transplantation – a single institutional experience in Taiwan. Ann Hematol. 2015;94:107–15.

18 Kapoor P, Rajkumar SV. Update on risk stratification and treatment of newly diagnosed multiple myeloma. Int J Hematol. 2011;94:310–20.