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Real-World Clinical Outcomes in Elderly Chinese Patients with Multiple Myeloma: A Single-Center Experience

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Background: Recently, improvement in overall survival (OS) was demonstrated in elderly patients with multiple myeloma (MM). Our aim here was to analyze treatment outcomes in elderly Chinese patients with MM in real-world practice.





Material/Methods: This retrospective study enrolled 122 newly diagnosed MM patients ages 65–84 between January 2007 and December 2015 in a single hematology department.

Results: The median age of patients was 70.5 years. The median OS period of the entire cohort was 33 months; the 5-year OS estimate was 30.4%. The median OS of the 65–69, 70–74, and ≥75 years old groups were 43, 36, and 6 months, respectively. Female patients had better OS than male patients (40 and 28 months, $P=0.026$). Patients who received short-course bortezomib-containing regimens during their course of disease had a significantly longer median OS of 37 months compared with 28 months for patients without bortezomib treatment ($P=0.029$). Patients with age-adjusted Charlson comorbidity index (aaCCI) <5 showed longer median OS compared to those with aaCCI ≥5 (45 months vs. 23 months, $P<0.001$). Multivariate analysis revealed that male sex, high aaCCI, and LDH were independent prognostic factor for OS.

Conclusions: The marked survival improvement in the elderly patients was associated with the increased use of short-course bortezomib. CCI and LDH are important clinical prognostic factors for survival in elderly MM patients.

MeSH Keywords: **Comorbidity • Multiple Myeloma • Survival Analysis**

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Background

Multiple myeloma (MM) is an incurable hematologic malignancy of plasma cells and mainly affects the elderly [1]. With increasing life expectancy and an aging population, the percentage of elderly patients will increase and the incidence of MM will also likely grow rapidly. In the last decade, the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) has dramatically increased overall survival (OS) in patients with MM [2]. In an analysis of the database of the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program up until the year 2004 [3], strong increases were seen in the age group younger than 59 years, whereas the effect in patients 60–69 years of age was only modest and no improvement was observed in patients over age 70 years of age. Interestingly, recent data suggest that the survival of MM patients age 65–74 years has improved over time, especially after 2006 [4,5].

Bortezomib is now an important component of anti-myeloma therapy in older myeloma patients. A phase III VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) trial involving patients aged 65 or older indicates that bortezomib, melphalan, and prednisone (VMP) produced a markedly higher response rate (CR: 30% vs. 4%, $P<0.001$; \geq PR 71% vs. 35%, $P<0.001$), longer time to progression (24.0 months vs. 16.6 months), and better 3-year OS (68.5% vs. 54%, $P=0.0008$) compared with melphalan and prednisone (MP) alone [6,7]. Another phase III study showed a less intensive induction with a bortezomib-based regimen, followed by maintenance, could reduce toxic effects while maintaining efficacy in elderly patients with untreated multiple myeloma [8].

Elderly MM patients, due to impaired performance status or comorbidities, are often excluded from clinical trials, and there is little evidence on how to translate results from cooperative studies to older or frail patients in real life. In addition, most of studies published to date are from Europe or North America, and there is limited information outside clinical trials on the effects of newer agents on outcomes in elderly Chinese patients with MM. Therefore, we retrospectively analyzed the clinical characteristics and outcome of elderly MM patients who were receiving clinical care at a medical center in China over the past 9 years.

Material and Methods

Patients and study design

This was a retrospective analysis of 130 consecutive elderly (≥ 65 years) patients who were newly diagnosed with symptomatic MM during a 9-year period between 1 January 2007

and 31 December 2015 in a typical regional university hospital. The last follow-up date was 31 December 2016. Eight patients were excluded from the analysis due to loss of follow-up data. Finally, a total of 122 patients were evaluated. Detailed data regarding these patients were collected using medical charts and electronic records. Data were collected with the following items: baseline demographics, clinical and laboratory data at diagnosis, and information concerning treatment and response. The age-adjusted Charlson comorbidity index (aaCCI) score was calculated according to the criteria reported by Charlson et al. [9,10].

The diagnosis and clinical staging of MM were based on the Durie-Salmon (DS) staging system and the International Staging System (ISS) [11,12]. The banded chromosomal analysis of the marrow cells was assessed in 78 patients. Because fluorescent *in situ* hybridization (FISH) was not available in our hospital, we had not performed cytogenetic risk stratification of the patients. Treatment for each patient was determined by the physician, the patient, or their family. All anti-myeloma treatment regimens consecutively used were recorded. Treatment responses were evaluated according to the International Myeloma Working Group (IMWG) criteria [13].

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 19.0). P -values <0.05 were considered significant. Continuous variables were summarized as median and extreme values and categorical data as absolutes and percentages. OS was calculated from the time of diagnosis of symptomatic myeloma to the time of death or last follow-up. Survival curves were plotted using the Kaplan–Meier method, with differences assessed with the log-rank test. A Cox regression model was used to analyze the risk factors for predicting OS. Parameters with $P<0.1$ in univariate analysis were further entered in multivariate analysis. A backward selection method was used to remove variables with a $P>0.05$. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI).

Results

Patient characteristics

Patient baseline characteristics are listed in Table 1. The median age of patients in this study was 70.5 (range, 65–84) years, 44.3% of patients were 65–69 years old, 31.1% were 70–74 years old, and 24.6% were older than 74 years. There were more men ($n=73$, 59.8%) and the major types of MM were IgG ($n=50$, 41%) and IgA ($n=42$, 34.4%). The conventional and novel drug protocols used as treatment are shown in Table 2. Novel agents were thalidomide, lenalidomide, and bortezomib.

Table 1. Patients' characteristics.

Characteristics	Total	
Number of patients	122	
Age of ≥75 years	30	(24.6)
Male	73	(59.8)
Myeloma type		
IgG	50	(41)
IgA	42	(34.4)
Light chain	20	(16.4)
Non-secretory	7	(5.7)
Others	3	(2.5)
DS stage		
II	12	(9.8)
III	110	(90.2)
ISS stage		
I	5	(4.1)
II	57	(46.7)
III	60	(49.2)
WHO performance status ≥3	60	(49.2)
aaCCI ≥5	50	(41)
Hemoglobin <10 g/L	96	(78.7)
Albumin <3.5 g/L	116	(96.7)
lactate dehydrogenase > normal	34	(27.9)
Creatinine >177 μmmol/L	52	(42.6)
Calcium >2.75 mmol/L	16	(13.1)

Data are presented as n or n (%). WHO – World Health Organization; aaCCI – age-adjusted Charlson comorbidity index.

Lenalidomide was approved for sale in China in June 2013, but it was approved only for treatment of relapsed or refractory myeloma patients [14]. Melphalan is not available in China. The median number of cycles of bortezomib treatment was 2 (range, 1–4). The main reasons for the short duration of bortezomib therapy were the high cost of treatment and the adverse effects. The median follow-up of all patients was 25.5 (range, 1–95) months, and 41 of 122 (36.6%) patients were alive at the time of data collection.

Table 2. The treatment of 122 myeloma patients.

Regimens	Initial therapy	Subsequent therapy
MP	1 (0.8)	5 (4.1)
VAD	22 (18)	13 (10.7)
Other regimens without novel agents ^a	23 (18.9)	26 (21.3)
VTD	42 (34.4)	12 (9.8)
PAD	13 (10.7)	6 (4.9)
Other bortezomib-based regimens ^b	2 (1.6)	7 (5.7)
TD	14 (11.5)	5 (4.1)
Other IMiD-based regimens ^c	5 (4.1)	5 (4.1)

Data are presented as n (%). MP – melphalan-prednisolone; VAD – vincristine-doxorubicin-dexamethasone; VTD – bortezomib-thalidomide-dexamethasone; PAD – bortezomib-doxorubicin-dexamethasone; TD – thalidomide-dexamethasone; IMiD – immunomodulatory drugs. ^a Other regimens without novel agents: cyclophosphamide-vincristine-melphalan-prednisolone (COMP); vincristine-pegylated liposomal doxorubicin-dexamethasone (DVD); cisplatin- etoposide-ifosfamide-dexamethasone (DECP); cyclophosphamide-vincristine-doxorubicin- dexamethasone (CVAD); dexamethasone. ^b Other bortezomib-based regimens: bortezomib-dexamethasone (VD); bortezomib-melphalan-prednisolone (VMP); bortezomib-lenalidomide-cyclophosphamide-dexamethasone (VRCD); VTD + allogenic cytokine-induced killer (allo-ClK). ^c Other IMiD-based regimens: melphalan-thalidomide-dexamethasone (MTD); lenalidomide-dexamethasone (RD).

Survival outcomes

The median OS period of the entire cohort was 33 months (95% CI; 25–41) and the 5-year overall survival estimate was 30.4%. As age is an important factor for survival, OS were calculated and compared according to the 3 age groups (Figure 1A) to assess the effect of age on survival. The median OS of the 65–69, 70–74, and ≥75 year age groups were 43, 36, and 6 months, respectively. Log-rank analysis indicated that the OS of the group age ≥75 years was significantly shorter compared to the other 2 age groups (65–69 vs. 70–74, $P=0.738$; 70–74 vs. ≥75, $P=0.001$; 65–69 vs. ≥75, $P=0.000$). Female patients had better OS compared to male patients (40 and 28 months, $P=0.026$; Figure 1B). Female patients also had a 5-year survival rate of 42.1% vs. 21.7% for male patients.

We then explored the impact of short-course bortezomib therapy on survival outcomes. Sixty-seven patients (54.9%) were treated with bortezomib; 57, 29, and 15 patients received bortezomib as frontline therapy, salvage therapy, or in both

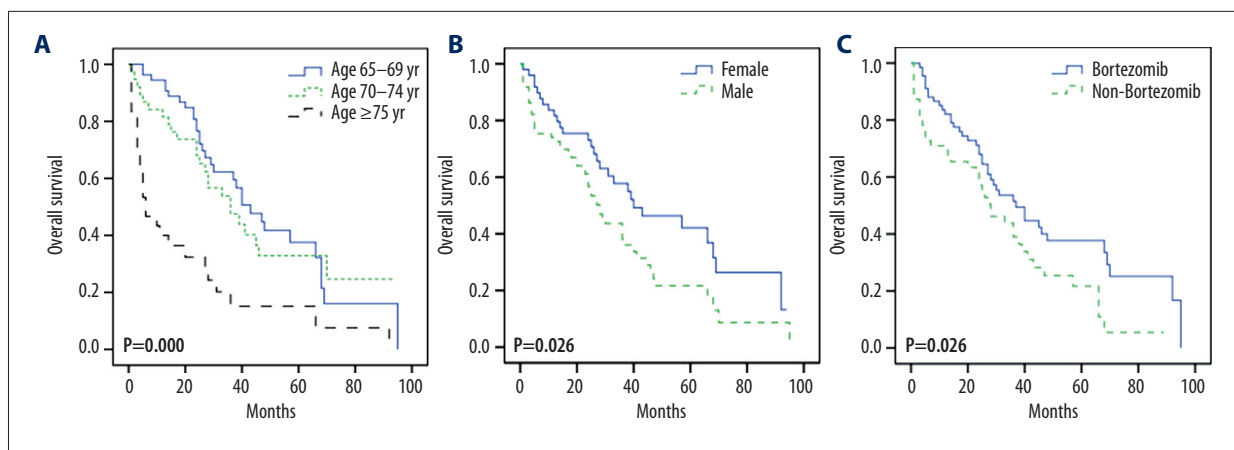


Figure 1. Analysis of survival in elderly patients with MM. (A) OS according to the different age groups. (B) OS according to sex. (C) OS according to therapy.

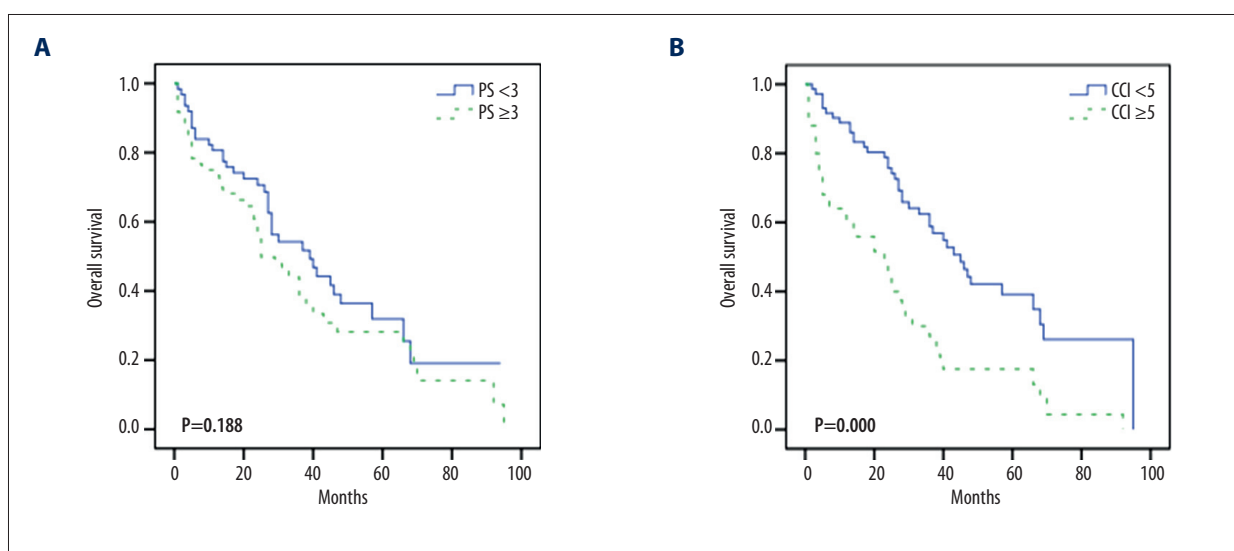


Figure 2. Analysis of survival in elderly patients with MM. (A) OS according to PS. (B) OS according to CCI.

settings, respectively. As shown in Figure 1C, patients who received bortezomib-containing regimens during their course of disease had a significantly longer median OS of 37 (95% CI, 25–49) months compared with 28 (95% CI, 18–38) months for patients without bortezomib treatment ($P=0.029$).

We further examined the survival of patients according to PS ≥ 3 and aaCCI ≥ 5 (Figure 2). Notably, there were no major differences in OS between patients with PS < 3 and PS ≥ 3 , with median survival times of 39 months and 25 months ($P=0.188$), respectively. Patients with aaCCI < 5 showed longer median OS compared to those with aaCCI ≥ 5 (45 months vs. 23 months, $P<0.001$).

Prognostic factor for OS

Using univariate and multivariate analyses, we investigated clinical variables to identify factors affecting OS (Table 3).

According to univariate analysis, we found that age ≥ 75 years, hemoglobin < 10.0 g/L, aaCCI ≥ 5 , and serum LDH $>$ normal were associated with inferior OS. In the multivariate analysis, male sex ($P=0.048$), aaCCI ≥ 5 ($P=0.005$), and serum LDH $>$ normal ($P=0.03$) were significantly and independently associated with OS.

Discussion

We examined the clinical features and treatment outcomes of consecutively enrolled, elderly, newly diagnosed MM (DNMM) patients during a 9-year period at a single institution. Among 122 MM patients, 30 patients (24.6%) were older than 75 years. Interestingly, there was a higher proportion (90.2%) of patients with DSS stage III. However, only 49.2% of patients were classified into stage III myeloma by ISS. Because older

Table 3. Univariate and multivariate analysis of factors associated with overall survival.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (yr) ≥75	4.373 (1.409–13.566)	0.011	2.327 (0.661–8.192)	0.189
Man	1.987 (0.925–4.27)	0.078	2.307 (1.009–5.277)	0.048
IgA	1.422 (0.632–3.195)	0.395		
ISS III	1.024 (0.483–2.172)	0.95		
WHO performance status ≥3	1.953 (0.909–4.199)	0.086	1.966 (0.841–4.597)	0.119
Charison comorbidity score ≥5	3.644 (1.545–8.597)	0.003	3.612 (1.482–8.802)	0.005
Hemoglobin <10 g/L	2.429 (1.001–5.889)	0.05	2.146 (0.81–5.684)	0.124
Albumin (g/L) <3.5 g/L	2.053 (0.396–10.652)	0.392		
Lactate dehydrogenase > normal	3.082 (1.157–8.208)	0.024	3.137 (1.117–8.809)	0.03
Creatinine >177 μmmol/L	2.0 (0.909–4.403)	0.085	0.753 (0.277–2.049)	0.579
Calcium >2.75 mmol/L	0.822 (0.276–2.444)	0.724		

ISS – international staging system; DSS – Durie-Salmon staging system; WHO – World Health Organization; OR – odds ratio; CI – confidence interval.

patients usually have more complications and similar symptoms, many of them do not come to the clinic until the disease becomes more severe [15]. It is possible that the disease severity was overestimated by the DSS staging systems due to severe anemia or advanced bony lesions.

MM is known to be a disease commonly occurring in older people. Age is one of the most important prognostic factors in the treatment of myeloma. Our study showed a significant age-dependent survival rate in MM patients. We also found that patients aged 65–74 years had better median OS compared with elderly (≥75 years of age) patients, in accordance with previously published studies [4,5]. Female patients also showed a longer OS, with a 5-year survival rate of 42.1% vs. 21.7% for male patients, and this difference was statistically significant.

As expected, in the present study, first-line therapy with short-course bortezomib-based regimens significantly improved the overall response rate (ORR) and ≥ very good partial response (VGPR) when compared with non-bortezomib regimens [16], but the high ORR and VGPR rate were not reflected in the survival advantage in elderly NDMM patients (data not shown). However, patients treated with short-course bortezomib-based regimens during their course of disease had a significantly longer OS than those treated without it. We found that improvement in OS was associated with the increased use of bortezomib in salvage therapy. This observation is in line with recently published reports on the outcomes of elderly MM patients after the introduction of bortezomib [17,18].

The largest epidemiological study of MM conducted in China is that of Lu et al. [19], published in 2014, which analyzed 940 NDMM patients at 3 major myeloma centers from January 2008 to December 2011, with an average 21-month follow-up (range, 1–63 months). The median age was 59 years. FISH results were collected in 47.02% of patients. Median OS and progression-free survival (PFS) for all patients were 54 and 26 months, respectively. Regarding age, 31.5% patients were older than 65 years; their median OS was 46.07 months, and PFS was 21 months. These older patients had inferior survival compared with patients younger than 65 years. The median OS for patients who received the bortezomib-containing regimen was 58 months and 49.8% of cases treated with bortezomib as first-line regimen had better OS compared with those treated without it. There were PFS benefits in younger patients receiving bortezomib, but not in older ones. There was no significant difference in OS between younger and older patients. Significant factors for survival by multivariate analysis were sex, ISS stage, number of FISH abnormalities, and extramedullary disease [19]. Although the median bortezomib cycles were not reported, the authors stated that the patients may have stopped treatment before the maximum response had been reached due to economic reasons, especially among patients receiving bortezomib, and survival may have been affected by this [19]. An et al. reported the clinical features and treatment outcomes of 61 MM patients over age 65 years treated at a Chinese tertiary hospital between March 2006 and March 2012, with average follow-up of 38 months (range, 24–96 months) [20]. The median age was 72.5 years and 21.3% of patients had FISH results. The median OS of the age 65–74 and ≥75 years groups were 37 and 19 months, respectively.

There was a mean of 4 cycles of bortezomib-based regimens used. For patients who received bortezomib-containing regimens as first-line therapy, the median OS and PFS were 41 and 23 months, respectively. Age and MM with EMP had a negative impact on survival [20]. In this study, there was no significant survival advantage in older NDMM patients from bortezomib therapy. Our results are consistent with theirs [19,20]. The high remission rate in first-line therapy with bortezomib did not translate into a survival benefit in elderly NDMM patients.

Apart from disease-related factors, patient-related factors have also been described to affect the outcome of treatment of MM [21–24]. Because age is associated with increased comorbidities and diminished functional status, stratification of older patients according to comorbidity and disability may greatly assist in selecting an optimal therapy and developing personalized therapies to balance benefits and toxicity. CCI is widely used in clinical practice because it is simple and convenient [9,10,25]. In line with other studies [22,24], our study demonstrated that poor aaCCI was significantly associated with short survival. Multivariate analysis revealed high aaCCI was an independent prognostic factor for OS. The aaCCI ≥ 5 as a cutoff value clearly stratified the outcome of elderly MM patients. Unexpectedly, lack of an association between PS and OS was seen in our analysis. This may be partially because the high PS scores of patients could be due to myeloma; thus, the PS improved after administration of active therapy.

Our single-center study has some limitations. First, it was retrospective and had a small sample size. Second, there might be potential bias in the choice of initial therapy, and treatment regimens and schedules were relatively heterogeneous. In addition, data on fluorescence *in situ* hybridization (FISH) or cytogenetics were lacking in our cohort. However, our results are from a real patient cohort of MM in a developing country, where most new therapies are out of reach for most patients.

Conclusions

This study confirmed that the marked survival improvement in elderly Chinese patients was associated with increased use of short-course bortezomib. Our study showed that patients with aaCCI ≥ 5 and serum LDH $>$ normal at diagnosis had significantly shorter OS. CCI and LDH are important clinical prognostic factors for survival in elderly MM patients and might be useful to guide personalized therapy in future analyses.

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Conflict of interest

None.

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