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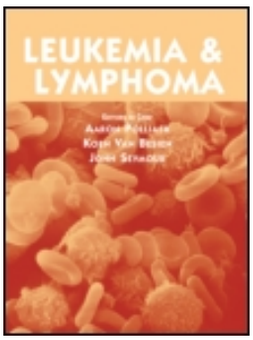

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ORIGINAL ARTICLE: CLINICAL

Clinical features and treatment outcome of very elderly patients over 80 years old with multiple myeloma: comparison with patients in different age groups in the era of novel agents

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Abstract

We retrospectively analyzed the outcomes of 175 consecutive patients admitted to our hospital between April 2004 and June 2014, and identified 42 (24%), 80 (46%), and 53 (30%) patients ≥80, 66–79, and ≤65 years old, respectively. The median progression-free survival (PFS) and overall survival (OS) of the ≥80, 66–79, and ≤65 years old groups were 19.1, 26.3, and 54.3 months, and 31.9, 54.8, and 83.8 months, respectively. Patients ≥80 but not ≤79 years old with ECOG performance score (PS) ≥3 and/or Charlson comorbidity index (CCI) ≥5 showed significantly shorter survival. ECOG PS and CCI predicted the treatment outcome of patients ≥80 but did not predict ≤79 years old.

Keywords: Age, comorbidity, 80 years old, multiple myeloma, performance status, survival

Introduction

The incidence rate of multiple myeloma (MM) increases with age. MM is a disease of the elderly with a median age of presentation in the early 70s [1,2]. Although somewhat arbitrary, the World Health Organization (WHO) defines "elderly" as older than a chronological age of 65 years. Aging is a highly heterogeneous phenomenon, and life expectancies of people 70 and 80 years old vary from 6.7–18.0 years and from 3.3–10.8 years, respectively [3]. A steady increase has been reported in the incidence of MM, as anticipated by the increase in life expectancy [4], especially in developed countries, although patients with advanced age, especially ≥80 years old, are often excluded from clinical trials due to poor performance status (PS), multiple comorbidities, and socioeconomic reasons [5]. In addition, patients treated in referral centers and those who are included in clinical trials often represent a selected patient population. As patients ≥80 years old account for a considerable proportion of MM cases, they have been treated with novel non-cytotoxic agents, such as thalidomide, bortezomib, and lenalidomide. However, limited information is available regarding the clinical characteristics and treatment outcomes in this group of patients [6,7]. Furthermore, it is unclear whether previously identified prognostic factors are of value in elderly patients in the era of novel agents. In addition, most previous clinical studies often excluded elderly patients due to impaired performance status or impaired renal function, and were performed in large myeloma centers or as collaborations between large numbers of institutions. These data may not represent the clinical features or treatment outcomes in patients with myeloma in actual daily practice. Our hospital (Kameda General Hospital, Kamogawa-shi, Chiba, Japan) is a large hospital in a rural city, Kamogawa-shi, which is located 60 miles south east of Tokyo, and almost all patients with myeloma in this area are referred to this hospital. To clarify these issues, we compared the clinical characteristics and treatment outcomes of all consecutive patients admitted and treated at our hospital among different age groups (≥80, 66–79, and ≤65 years old) over the past 10 years.

Methods

A total of 184 consecutive patients with newly diagnosed symptomatic MM admitted to Kameda Medical Center from April 2004 to June 2014 were retrospectively analyzed. Nine patients who refused or did not receive treatment (four patients in the ≥80, four patients in the 66–79, and one patient in the ≤65 years old group) for at least 2 months were excluded from the study, but patients who received at least one course of treatment were included even if the treatment was discontinued early due to adverse events or death. Patients with concomitant light chain amyloidosis who fulfilled the criteria for symptomatic myeloma diagnosis [8]

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were included. Finally a total of 175 patients were analyzed. Treatment responses were evaluated according to the international uniform response criteria for multiple myeloma [9]. The reduction or suspension of treatment was determined according to the decision of the physician, the patient, or their family.

Multiple baseline characteristics of the patients consisting age, sex, European Cooperative Oncology Group (ECOG) performance status (PS) [10] at presentation, hemoglobin, lactate dehydrogenase (LDH), albumin, serum free light chain (FLC), β_2-microglobulin, and international staging system (ISS) were collected from the medical records. Comorbidities at presentation, including cardiac disease, pulmonary disease, renal disease, psychiatric or neurological disease, and diabetes (Charlson comorbidity index [CCI]) [11], were retrospectively assessed from medical records. Serum FLC level at baseline was available in 170 patients (97%). High-risk cytogenetic features were investigated by fluorescence in situ hybridization (FISH) using probes for t (4;14), del(17p), and t(14;16) on bone marrow samples at presentation or at relapse. Response to treatment was assessed by the International Myeloma Working Group (IMWG) criteria [9,12]. Progression-free survival (PFS) was defined as the time from the start of any kind of treatment to the date on which progression from best response or death occurred, whichever came first. Overall survival (OS) was calculated from the time of first diagnosis of symptomatic myeloma to the time of death. Discontinuation of treatment was defined as more than 6-month discontinuation of any anti-myeloma agents for any cause despite progression of the disease. Patients were divided into three groups: ≥ 80 years old, 66–79 years old, and ≤ 65 years old. Multiple baseline clinical characteristics and laboratory data were evaluated and comparisons were performed among the three groups.

Due to the retrospective nature of this study, written informed consent was not obtained from the patients diagnosed before April 2010, but was obtained from all of the patients treated thereafter. This study was approved by the Institutional Review Board at Kameda Medical Center in keeping with the Declaration of Helsinki.

Statistical analysis

Clinical baseline characteristics of three groups were described as mean ± SD for normal distributed continuous variables and median (interquartile range) for non-normally distributed variables. Categorical variables were described as percentages. The distribution of continuous variables in three groups was compared by Analysis of Variance for normal distributed variables and by Kruskal-Wallis test for non-normal distributed variables. Kaplan-Meier survival curves were constructed, and difference of survival rates was tested by log-rank test. All statistical analyses were performed by R version 3.0.2.

Results

Baseline characteristics

Table I shows the clinical and laboratory characteristics and treatments according to the different age groups. The percentages of patients with age ≥ 80 years, 66–79 years, and ≤ 65 years were 24.2%, 45.1%, and 30.6%, and the median ages of the corresponding groups were 85, 72, and 60 years old, respectively. When the patients were divided according to the period of admission between April 2004 to March 2008, April 2008 to March 2012, and April 2012 to July 2014, the percentages of patients ≥ 80 years old in each period were 27.1%, 35.6%, and 37.3%, respectively. This steady increase in patients ≥ 80 years old may reflect the increase in life expectancy of the elderly population, especially in rural areas. The median observation period of patients ≥ 80 years old was shorter than those of the other groups due to their recent increase of proportion, lower response rate, and poorer outcomes. Patients with ECOG PS ≥ 3 and CCI ≥ 5 were more frequent in the older age groups. Percentages of patients with PS ≥ 3 and CCI ≥ 5 in those ≥ 80 years old, 66–79 years old, and ≤ 65 years old were 52.4% and 38.5% ($p = 0.003$), 16.3%

Table I. Comparison of patient characteristics and treatments in different age groups.

	Total $n = 175$			
	≧80 yr (%)	66~79 yr (%)	≦65 yr (%)	p-value
Number of patient	$n = 42$ (24.2)	$n = 80$ (45.1)	$n = 53$ (30.6)	
Median age (yr)	85	72	60	NA
Male	19 (48.5)	46 (58.0)	32 (60.4)	0.291
Median observation period (months; range)	20.4; 1.9–54.6	28.6; 1.1–126.7	33.5; 3.0–127.1	NA
PS status ≥ 3	22 (52.4)	30 (38.5)	10 (16.3)	0.003
Charlson comorbidity score ≥ 5	22 (52.4)	25 (32.1)	0 (0%)	< 0.001
Non-IgG type	17 (59.3)	38 (50.0)	27((49.1)	0.59
Hemoglobin < 10 gr/dl	28 (66.7)	48 (60.8)	32(60.4)	0.774
Albumin < 3.5mg/dl (%)	35 (83.3)	49 (62.0)	26 (49.1)	0.003
LDH > normal	11 (26.2)	20 (25.0)	12 (22.6)	0.924
Creatinine > 2mg/dL	8 (19.0)	21 (26.6)	12 (22.6)	0.636
Baseline sFLC > 1000 mg/L (%)	16[1] (41.2)	45[2] (58.4)	27[3] (49.1)	0.265
β2 MG > 3.5 mg/L	35 (83.3)	52 (65.0)	32 (60.4)	0.043
ISS stage 3	29 (69.0)	43 (54.4)	26 (49.1)	0.134
Other cancer	10 (23.8)	12 (15.4)	2 (3.6)	0.017
High risk cytogenetics*	6[4] (16.7)	16[5] (25.8)	18[6] (39.1)	0.044
Use of bortezomib or lenalidomide at any time	40 (95.2)	78 (97.5)	53 (100)	0.3
Death within 12 months	7 (11.9)	10 (12.8)	3 (5.4)	0.226
Stem cell transplantation	0 (0)	4 (5.1)	30 (54.5)	< 0.001

*Any of del 17, t(4;14), or t(14;16).
Number of patients examined: [1]39, [2]77, [3]54, [4]36, [5]62, [6]46.

Table II. Treatment response of patients with different age group.

Treatment response	≧80 yr of age $n=42$ (%)	66~79 yr of age $n=80$ (%)	≦65 yr of age $n=53$ (%)	p
CR	9 (21.4)	26 (32.5)	23 (43.3)	0.083
VGPR	11 (26.2)	19 (23.8)	19(35.8)	0.309
PR	17(40.5)	26 (32.5)	7 (13.2)	0.006
SD or less	5 (11.9)	9 (11.2)	4 (7.5)	0.771
% ≧VGPR	20 (47.6)	45 (56.2)	42 (79.2)	0.003

CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease.

and 52.4%, and 32.1% and 0% ($p<0.001$), respectively. There were no differences in myeloma heavy chain type, hemoglobin concentration, or LDH, but significant differences were noted in serum albumin and β_2-microglobulin between the three groups. Although the number of patients with ISS 3 was higher among the older patients, the differences across groups were not significant. The rate of coincidence of other cancers in patients ≥ 80 years old was 23.8%, which was significantly higher than in the other groups.

The incidences of high-risk cytogenetics determined by FISH, any of del 17, t(4;14) and t(14;16), were significantly higher in younger patients. All the patients received novel agents, including thalidomide, bortezomib, and lenalidomide; however, there were four patients who died before August 2007 who did not receive either bortezomib or lenalidomide because of unavailability of those agents in Japan. Stem cell transplantation was performed in 30 patients (56.6%) ≤ 65 years old and in four patients (5%) 66–79 years old.

Treatment outcome

Table II shows the treatment outcomes of the three groups of patients. Although not statistically significant, CR rate was lower in older patients (≥ 80, 66–79, and ≤ 65 years old; 21.4%, 32.5%, 43.3%, respectively, $p=0.083$). The proportion of patients with ≥ VGPR was significantly lower in the advanced age group.

At a median follow-up of 29 months (range: 2–107 months), median durations of progression-free survival (PFS) and overall survival (OS) for the whole patients were 28.8 months and 54.6 months, respectively. To explore the impact of age on survival, PFS and OS were calculated and compared according to the three age groups (Figure 1). The median PFS of the ≥ 80, 66–79, and ≤ 65 years old groups were 19.1, 26.3, and 54.3 months, respectively. Log-rank analysis indicated that the PFS of age ≥ 80 years old was significantly shorter compared to the other two age groups (≤ 65 vs 66–79, $p=0.057$; 66–79 vs ≥ 80, $p=0.033$; ≤ 65 vs ≥ 80, $p=0.0009$). These differences in PFS among the three age groups were translated to differences in OS. The median OS of the ≥ 80, 66–79, and ≤ 65 years old groups were 31.9, 54.8, and 83.8 months, respectively.

Death within 2 months and 12 months from admission occurred in two (4.8%), one (1.3%), and 0 (0%), and 17 (11.9%), 10 (12.8%), and three (5.4%) patients in the ≥ 80, 66–79, and ≤ 65 years old groups, respectively. The most common cause of death within 12 months in patients ≥ 80 years old was infection (3/7), but it was associated with disease progression in patients 66–79 years old (6/10) and cardiac failure due to amyloidosis (2/3) in patients ≤ 65 years old.

As a subset of elderly patients without a favorable initial response may die relatively early due to poor PS and/or comorbidity, these patients may not show a favorable response. Therefore, we analyzed the survival of patients according to the myeloma response better than VGPR, PS ≥ 2, and CCI ≥ 5. PFS and OS of patient ≥ 80 years of age who achieved better than VGPR had significantly better PFS and OS (median PFS and OS in patients ≥ VGPR vs < VGPR were 21.3 month vs 6.8 months and 30.4 months vs 16.0 months, respectively). A landmark analysis at 6 months, to allow for sufficient duration of therapy, revealed a median OS from diagnosis of 30.4 months and 18.8 months for patients ≥ 80 years of age with and without better than VGPR, respectively ($p=$ 0.001) (Figures were not shown).

Figure 2 shows the OS rates of patients ≥ 80 years old according to the ECOG PS and CCI. Both patients with ECOG PS 0–1 and CCI 0–4 showed better OS compared to those with PS 3–4 and CCI ≥ 5 (median OS of patients with PS ≤ 2 vs > 3 and CCI < 4 vs ≥ 5 was 35.1 months vs 22.6 months

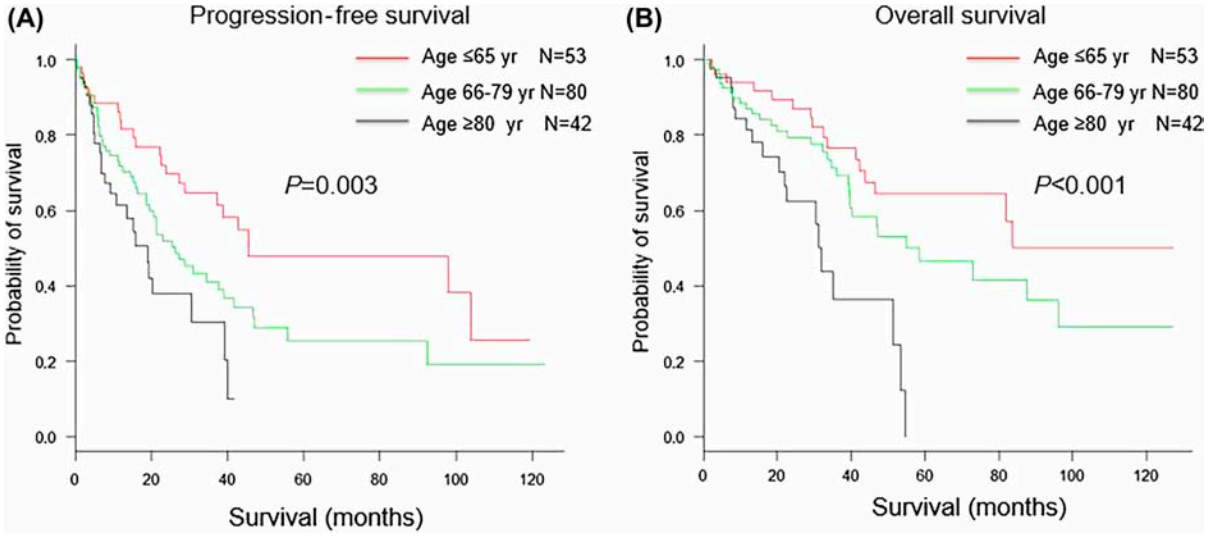

Figure 1. Survival of patients according to the different age groups (A) Progression-free survival (B) Overall survival.

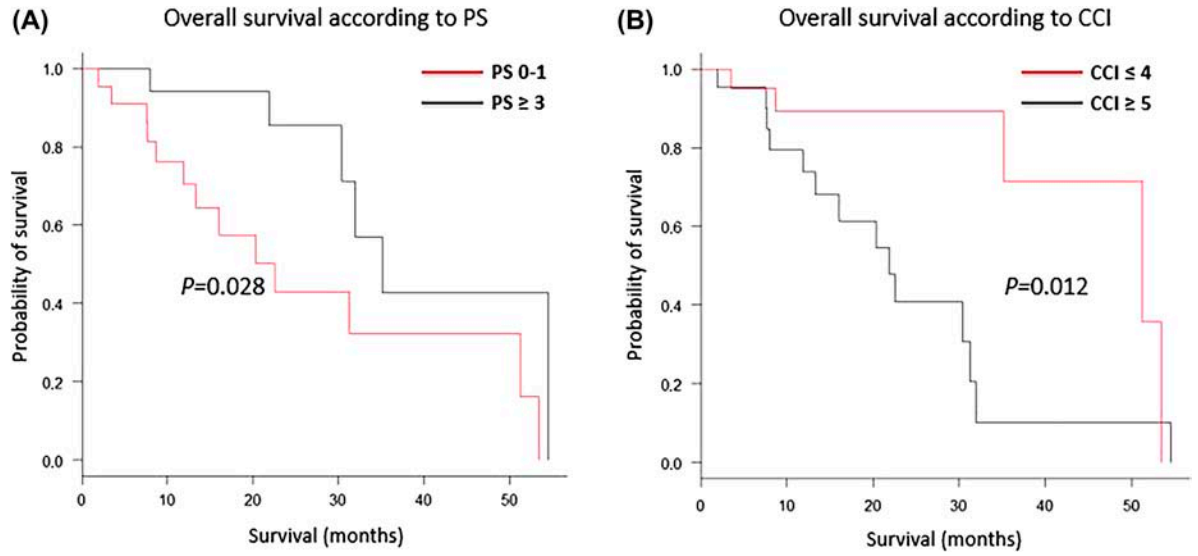

Figure 2. Overall survival of patients with age ≥ 80 years according to the performance status (PS) and Charlson's comorbidity index (CCI) (A) Overall survival according to PS (B) Overall survival according to CCI.

and 51.2 months vs 21.9 months, respectively). However, in patients 66–79 years old, OS was not different according to PS and CCI (Figure 3). Similar observations on PS were also made in patients ≤ 65 years old ($p = 0.058$, data not shown), but comparison was not possible on CCI due to the lack of patients CCI ≥ 5. These observations indicated that PS and CCI affect the survival of patients ≥ 80 years old, but may not have an effect in the other age groups.

Next, we postulated that patients ≥ 80 years old who achieved good myeloma response may have comparable survival to those in the younger age groups. We pooled the patients who obtained CR and VGPR and compared survival among the three groups (Figure 4). The numbers of patients who obtained more than VGPR in the ≥ 80, 66–79, and ≤ 65 years old groups were 20 (47.6%), 42 (52.5%), and 45 (84.9%), respectively. The median PFS and OS for patients who achieved better than VGPR who were ≥ 80, 66–79, and ≤ 65 years old was 39.3, 46.8, and 97.8 months and 53.4 months, not reached, not reached, respectively. These differences were not statistically significant ($p = 0.093$ and 0.184, respectively). These observations suggested that even patients ≥ 80 years old could have comparable PFS and OS if they could obtain favorable myeloma response better than VGPR.

Discussion

Advanced age is a negative prognostic factor in patients with cancer, including those with MM. MM is a disease of the elderly, and most patients with newly diagnosed MM are more than 65 years old. Our current study indicated the significant age dependency of survival in patients with MM. Among 180 MM patients admitted over a 10-year period in our cohort, 46 patients (25.6%) were over the age of 80 years

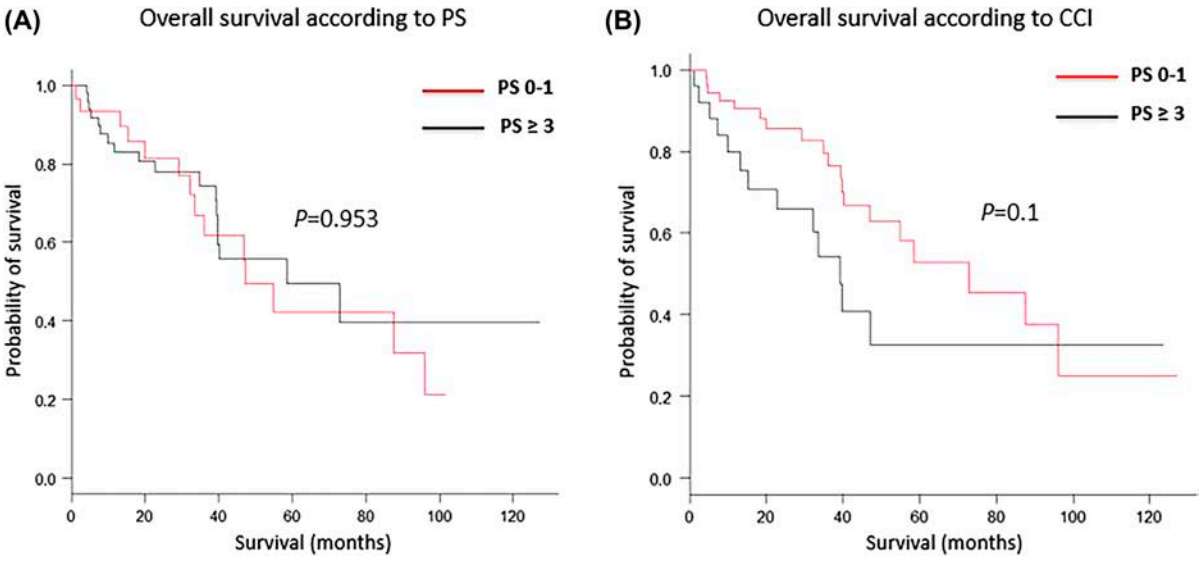

Figure 3. Overall survival of patients with age 66–79 years according to the performance status (PS) and Charlson's comorbidity index (CCI) (A) Overall survival according to PS (B) Overall survival according to CCI.

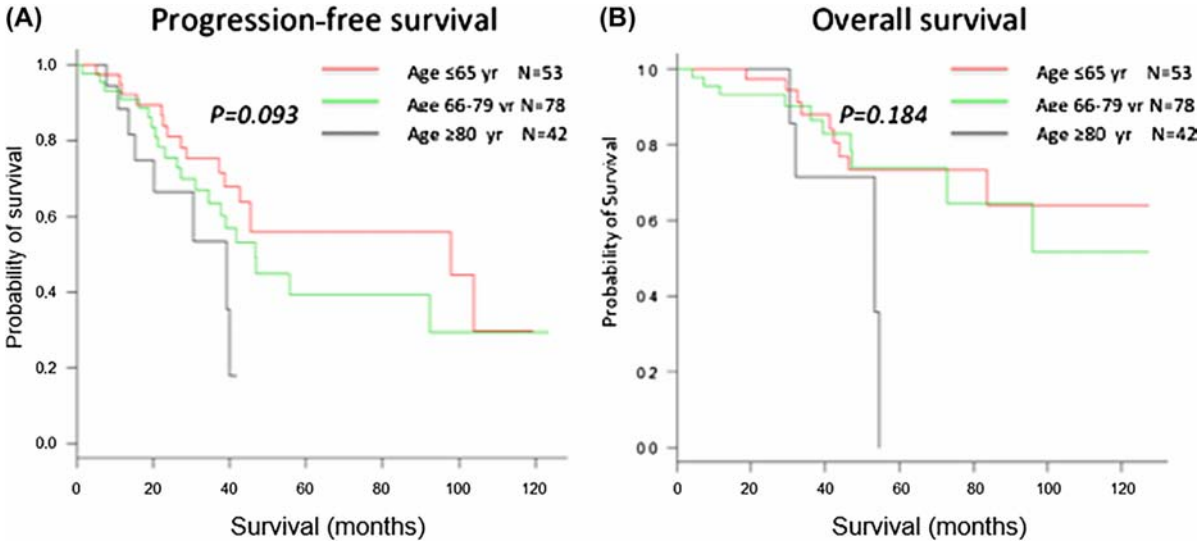

Figure 4. Progression-free and overall survival of patients who achieved better than VGPR according to the different age group.

and 81 patients (45.0%) were 66–79 years old. In this analysis, we included all of the unselected consecutive patients who received at least one cycle of chemotherapy or were treated with anti-myeloma agents for at least 2 months at our hospital. The percentage of patients with MM ≥ 80 years old treated at our hospital increased rapidly from 17% (13/77) during the period between April 2004 and March 2007, reaching 32% (33/103) during the period between April 2010 and July 2014. Although this figure may be different from the reports of tertiary center hospitals or large institutions [13,14], a recent report from Malmö University, Sweden, indicated that median age at diagnosis and proportion of newly diagnosed patients of MM more than 80 years old increased from 70–74 years and from 15–31%, respectively [15]. Therefore, we believe that our results are representative of real cohorts seen in clinical practice when treating MM patients in a rural area in our country. Our data reflect the rapid rise of the geriatric population in Japan, especially in rural areas. Dimopoulos *et al* [7] recently reported the incidence and clinical features of 682 patients from the database of the Greek Myeloma Study Group (GMSG). They reported that 155/682 (23%) of patients with MM were more than 80 years of age. The median survival period of patients more than 80 years old was 22 months, and 14% died within 2 months from start of therapy in their study. Bang *et al* [16] reported the treatment pattern and outcomes of 122 MM patients > 75 years old treated at the Mayo Clinic (Rochester, MN, USA). Novel agents (thalidomide, bortezomib, lenalidomide) were administered to 35% of patients as first-line therapy and 13 patients (34.3%) obtained better than VGPR. In our series, 20 of the 42 patients (47.6%) ≥ 80 years old obtained better than VGPR and their median survival period was 31.9 months. Seven patients (11.9%) died within 12 months, and only one patient died (2.4%) within 2 months.

The present study was performed to investigate the disease-specific and patient-related factors affecting the outcome of treatment of myeloma in different age groups. Patient-related factors include renal impairment, impaired PS, and comorbidities, such as decreased cardiac function, pulmonary function, diabetes, vascular diseases, and neurological deficit as indicated by CCI. As expected, PFS and OS were significantly shorter in patients with advanced age (Figure 1). Among the patients ≥ 80 years old, patients with better than VGPR showed significantly longer PFS and OS compared to those without. Similar observations were also made in patients 66–79 years old and ≤ 65 years old (data not shown). When patients that obtained better than VGPR were pooled in the respective age group and compared, PFS and OS did not differ significantly among the three groups ($p = 0.039$ and $p = 0.184$, respectively) (data not shown). These observations highlight the importance of obtaining a favorable response, such as VGPR or CR, not only in younger patients but also in those ≥ 80 years old.

PS and CCI clearly stratified the outcome of patients ≥ 80 years old. Patients with PS ≥ 3 and CCI ≥ 5 showed significantly inferior survival compared to those with better PS and CCI. Unexpectedly, however, these factors did not affect the treatment outcome in patients ≤ 79 years old, although comparison was not performed on CCI in those ≤ 65 years old due to the absence of patients with CCI ≥ 5 in this group. This may be partly explained by the fact that impairment of PS and CCI in younger patients could be due to myeloma, therefore, the PS and CCI improved after administration of anti-myeloma treatment. However, the situations may be more complex in elderly patients; impairment of PS and/or CCI in elderly patients comes from not only MM but also from other factors associated with aging itself. Our observations suggest that PS and CCI may predict outcome for patients ≥ 80 years old but not in younger patients.

ISS has been utilized as a useful prognostic predictor in patients with myeloma, and has been validated not only in patients treated with conventional agents but also with novel agents [17]. However, ISS uses only disease-specific prognostic factors for prediction of outcome and the median age of the patients used for analysis was 60 years old; patients of advanced age with MM carry more complex factors, such as comorbidities, disabilities, and frailty, in addition to their chronological age. Palumbo *et al* [18,19] proposed personalized therapy according to age and vulnerability in patients of advanced age. They emphasized the importance of tai-

lored treatment according to comorbidities, disabilities, and frailty. Although still preliminary and based on the experience of a single institution, our observations in the present study indicate that incorporation of PS and CCI assessments allows more adequate decision making in the treatment of elderly patients with MM. Patients ≥ 80 years old with good PS and lower CCI showed favorable outcome and are good candidates for active therapy in the era of novel agents.

The limitations of this study include its retrospective nature and small sample size. Treatment was not predetermined and was left to the discretion of the attending physician. In particular, the small size of the study population did not allow meaningful comparison of factors which may have an effect on the outcomes of elderly patients ≥ 80 years. However, our results represent the real patient cohort of MM in developing countries. We believe that the growing number of patients in the aging population, especially octogenarians, will highlight the importance of research regarding adequate care for this population not only in myeloma but also other cancers.

In conclusion, we showed that patients ≥ 80years old, but not ≤ 79 years old, with PS ≤ 2, CCI ≤ 4 at diagnosis and achieving myeloma response ≥ VGPR showed better PFS and OS among those of advanced age, even in patients ≥ 80 years old. We believe that patients with advanced age should not be denied the benefits of treatment if they are physiologically and mentally able to withstand the stress associated with treatment. ECOG PS and CCI predicted the treatment outcome of patients ≥ 80 but not ≤ 79 years old

Authorship statement

KM designed the study collected the data, and wrote the manuscript. YM performed the statistical analysis and wrote the manuscript. MF, KF, YS, HS, and MT provided clinical care and performed laboratory examinations. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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