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ORIGINAL ARTICLE

Pre-existing diabetes mellitus in patients with multiple myeloma

Yi-Sheng Chou[1,2†], Ching-Fen Yang[2,3†], Harn-Shen Chen[2,4], Sheng-Hsiang Yang[1,2], Yuan-Bin Yu[1,2], Ying-Chung Hong[1,2], Chun-Yu Liu[1,2], Jyh-Pyng Gau[1,2], Jin-Hwang Liu[1,2], Po-Min Chen[1,2], Tzeon-Jye Chiou[2,5], Cheng-Hwai Tzeng[1,2], Liang-Tsai Hsiao[1,2,6]

[1]Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]National Yang-Ming University School of Medicine, Taipei, Taiwan; [3]Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Division of Transfusion Medicine, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan

Abstract

Objectives: Type 2 diabetes mellitus is present in approximately 10% of patients at diagnosis of multiple myeloma (MM) and is associated with increased risks of adverse events caused by novel antimyeloma agents. However, the impact of type 2 diabetes on the survival of patients with MM has not been studied. *Methods:* We enrolled newly diagnosed patients with MM in Taipei Veterans General Hospital between 1999 and 2007 and identified those with pre-existing diabetes. The impact of pre-existing diabetes on patients with MM was evaluated by comparing clinical features, treatments and adverse reactions related to glycaemic control and overall survival (OS) of patients with and without pre-existing diabetes. *Results:* Of 310 patients with MM, 73% were men and 40 (12.9%) had pre-existing diabetes. Compared with their non-diabetic counterparts, MM patients with pre-existing diabetes had a significantly higher proportion of renal impairment [(RI), serum creatinine $\geq$2.0 mg/dL] and International Staging System stage III at diagnosis, and a significantly lower proportion of bisphosphonate use and a lower rate of RI reversal ($P = 0.087$). During the course of the disease, hyperglycaemia and hypoglycaemia of any grade were noted in 23 (67.6%) and 6 (17.6%) of these patients, respectively. Antidiabetic therapy was changed in 10 (29.4%) of 34 evaluable patients. MM patients with pre-existing diabetes had a significantly higher all-cause mortality risk (hazard ratio, 1.509; 95% confidence interval, 1.023–2.225, $P = 0.037$) compared with their non-diabetic counterparts. *Conclusions:* Our study demonstrated the impact of pre-existing diabetes on clinical features and OS in patients with MM.

Key words type 2 diabetes mellitus; hyperglycaemia; hypoglycaemia; multiple myeloma; all-cause mortality

Correspondence Dr. Liang-Tsai Hsiao, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Taipei 112, Taiwan. Tel: +886 2 28712121 ext 2507; Fax: +886 2 28757762; e-mail: lthsiao@vghtpe.gov.tw

[†]Both authors contributed equally.

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Multiple myeloma (MM) is prevalent in the elderly (1, 2), and pre-existing comorbidities are usually present at diagnosis (3). Among these comorbidities, type 2 diabetes mellitus (hereafter referred to as diabetes) is especially important because its incidence is anticipated to increase by 20% in developed countries between 2010 and 2030 (4). The prevalence of pre-existing diabetes in elderly patients with MM ranges from 6 to 11% (5–7). The clinical impact of pre-existing diabetes on patients with MM has been highlighted by the increased risk of peripheral neuropathy in clinical

trials using bortezomib (8–10). In addition, these patients have an increased risk of venous thrombosis if they receive thalidomide or lenalidomide (10–13).

However, this information may not be sufficient for clinicians in terms of the clinical features, management and prognosis of these patients. For example, myeloma-aggravating symptoms such as anaemia, proteinuria and even renal impairment (RI) (12) were also common in patients with type 2 diabetes. Furthermore, the use of steroid treatment as the backbone of conventional regimens against MM (14, 15) may cause additional harm to these patients in terms of glycaemic control, infection and outcome, especially for dexamethasone (16). In contrast to studies in solid tumours (17, 18), only a few epidemiological studies suggested that abnormal glucose metabolism was associated with an increased mortality from MM (19, 20). The current study analysed the impact of pre-existing diabetes on patients with MM in relation to clinical features and outcome by using a cohort of unselected Taiwanese patients who were characterized recently (21, 22).

Patients and methods

Patients

Consecutive patients with the diagnosis of MM between January 1999 and December 2007 in Taipei Veterans General Hospital were collected, as previously described (21, 22). The diagnosis of these plasma cell dyscrasias was made according to the commonly accepted criteria (23). The diagnosis of type 2 diabetes was based on the criteria of the respective period of diagnosis (24, 25). The presence of comorbid diabetes in our patients with MM was initially identified using the International Classification Diseases codes of 250–251 from the inpatient and outpatient records and subsequently validated by chart review. Pre-existing diabetes was noted when the diagnosis was made before or at the time of MM diagnosis. The ethics committee of Taipei Veterans General Hospital approved this study.

Clinical features, staging, treatment and survival of patients with MM

Data collection was performed by chart review, as described (21, 22). Briefly, data regarding clinical features and laboratory abnormalities at diagnosis were recorded. The cut-off level of abnormal laboratory tests was mainly defined according to those in the original study of the International Staging System (ISS) (26), except for serum total calcium (corrected) > 11.5 mg/dL as hypercalcaemia. The clinical stages were determined according to the Durie–Salmon (DS) staging system (27) and the ISS (26). The treatment modalities of MM and bisphosphonate use were reviewed. Before novel therapeutic agents became available in 2002, the major conventional chemotherapy regimens for these conditions were comprised of melphalan and prednisolone (MP) and vincristine, adriamycin and dexamethasone (VAD), as described (21, 22). High-dose therapy (HDT) and haematopoietic stem cell transplantation (HSCT) were usually administered to patients aged < 65 yr. The HDT regimens were melphalan (140 mg per square metre) and total body irradiation (7.5–8 Gy delivered in 3–4 fractions) before 2003 and melphalan (200 mg per square metre) since 2003. Patients with relapsed or refractory myeloma received salvage therapy in the form of thalidomide (since 2002) or bortezomib (since 2007). Because the analysis showed a higher proportion of RI [defined as serum creatinine (SCr) $\geq$ 2.0 mg/dL] in MM patients with pre-existing diabetes, the estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease formula: eGFR in millilitres per minute per 1.73 m^2 = 186 $\times$ $(SCr)^{-1.154}$ $\times$ $(age)^{-0.203}$ $\times$ (0.742, if female), in which SCr was the first value measured at diagnosis of myeloma. The degree of RI was classified according to the definition of chronic kidney disease (CKD) stages (28) as follows: stage 4, eGFR of 15–29 mL/min/1.73 m^2 and stage 5, eGFR < 15 mL/min/1.73 m^2 or under dialysis. RI reversal was evaluated and defined as (i) the fall of an initially elevated SCr concentration to the reference range, that is, 1.5 mg/dL (29, 30) or (ii) a decrease in SCr of at least 50% when the fall of SCr remained above 1.5 mg/dL in patients who did not undergo dialysis (31). OS was measured from the time of diagnosis to the date of death from any cause (i.e. all-cause mortality) or at the last follow-up in February 2010.

Glycaemic control and adverse effects

Data for diabetes-related complications and antidiabetic therapies before diagnosis of MM were collected. Data regarding the methods of glycaemic control after diagnosis of MM were collected for patients with available data who survived at least 1 month after diagnosis of MM. Regarding antidiabetic therapy, the choice of diet control, oral antidiabetic agents or insulin was dependent on the clinician's preference and decision. The antidiabetic therapy that was given in the steady state was recorded as opposed to the therapies that were used temporarily. In addition, the data of in-hospital laboratory-measured blood glucose and haemoglobin A1C (HbA1C) levels were collected, and adverse events related to glycaemic control such as hypoglycaemia and hyperglycaemia were evaluated using the National Cancer Institute Common Toxicity Criteria, version 4, as recommended (32). Hyperglycaemia was graded according to the level of blood sugar as follows: greater than upper limit of the reference range to 160 mg/dL (grade 1), >160 to 250 mg/dL (grade 2), >250 to 500 mg/dL (grade 3) and > 500 mg/dL or life-threatening consequences (grade 4). Hypoglycaemia was

graded according to the level of blood sugar as follows: < lower limit of the reference range to 55 mg/dL (grade 1), 55 –40 mg/dL (grade 2), 40–30 mg/dL (grade 3) and < 30 mg/dL or life-threatening consequences, or seizure (grade 4). The highest grade for each patient was recorded once. HbA1c was measured using high-performance liquid chromatography instruments (HLC-723G7; Tosoh Corp., www.tosoh.com) with a reference range of 4.2–5.8%.

Statistical analysis

To compare patients with and without pre-existing diabetes, the differences in clinical features and treatments were investigated using Pearson's chi-squared test. To determine RI reversal, landmark analysis was performed only for patients with SCr greater than the cut-off values at diagnosis who survived 1 month after diagnosis. Overall survival was analysed with the Kaplan–Meier estimate and log-rank test. Cox proportional hazards regression analyses were used to estimate OS [with 95% confidence intervals (CI)], with adjustment for several independent factors that had P values <0.1 at univariate analysis. The level of statistical significance was set at 0.05 for all tests. Statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical features and treatments of patients with MM in relation to pre-existing diabetes

A total of 310 patients (226 men and 84 women) with MM were included (Table 1). The median age at diagnosis was 71.8 yr, and 69.7% of patients were older than 65 yr. Forty patients (12.9%) were found to have pre-existing diabetes at MM diagnosis. Compared with their non-diabetic counterparts, patients with pre-existing diabetes had a significantly higher proportion of RI (defined as SCr $\geq$ 2.0 mg/dL;

Table 1 Clinical and laboratory features of 310 patients with MM in relation to the presence of pre-existing diabetes

Parameters	Overall (%)	Pre-existing diabetes		*P* value
		No (%)	Yes (%)	
No. of patients	310 (100)	270 (100)	40 (100)	–
Gender – male vs. female	226 vs. 84 (72.9 vs. 27.1)	199 vs. 71 (73.7 vs. 26.3)	27 vs. 13 (67.5 vs. 32.5)	0.41
Age, median (yr) (range)	71.8 (28–91)	71.7 (28–91)	72.5 (50–90)	0.305[1]
Age $\geq$ 65	216 (69.7)	187 (69.3)	29 (72.5)	0.677
Immunophenotype				
IgG	164 (52.9)	140 (51.9)	24 (60.0)	0.335
IgA	90 (28)	83 (30.7)	7 (17.5)	0.085
Light chain	53 (17.1)	44 (16.3)	9 (22.5)	0.331
WBC < 4000/μL	63 of 307 (20.5)	54 (20.2) of 267	9 (22.5)	0.740
Haemoglobulin < 10 g/dL	200 of 309 (64.7)	175 (65.1) of 269	25 (62.5)	0.752
Platelets < 130 000/μL	97 of 308 (31.5)	82 (30.6) of 268	15 (37.5)	0.381
Serum albumin < 3.5 g/dL	167 of 307 (54.4)	148 (55.4) of 267	19 (47.5)	0.348
Serum total calcium (corrected) > 11.5 mg/dL	52 of 307 (16.9)	43 of 267 (16.1)	9 (22.5)	0.315
Serum creatinine $\geq$2.0 mg/dL	101 (32.6)	80 (29.7)	21 (52.5)	0.004
Sβ_2 M $\geq$ 3.5 mg/L	241 of 300 (80.3)	207 of 261 (79.3)	34 of 39 (87.2)	0.249
Serum LDH > reference value	122 of 309 (39.5)	102 of 269 (37.9)	20 (50.0)	0.145
Stage – DS – I/II/III	21/67/222 (6.8/21.6/71.6)	18/60/192 (6.7/22.2/71.1)	3/7/30 (7.5/17.5/75.0)	0.791
Stage – ISS – I/II/III	43/87/169 of 299 (14.4/29.1/56.5)	39/82/139 of 260 (15.0/31.5/53.5)	4/5/30 of 39 (10.3/12.8/76.9	0.019
Induction chemotherapy				0.586
MP	129 (41.61)	111 (41.1)	18 (4.5)	
VAD like[2]	132 (42.6)	115 (42.3)	17 (42.5)	
Thalidomide[3]	85 (27.4)	76 (28.1)	9 (22.5)	0.455
Bortezomib[3]	32 (10.3)	26 (9.6)	6 (15.0)	0.297
HDT and HSCT[3]	36 (11.6)	34 (12.6)	2 (5.0)	0.162
Bisphosphonate[3]	245 (79.0)	219 (81.1)	26 (65.0)	0.019

[1]By Mann–Whitney test.
[2]Included VAD and high-dose dexamethasone alone.
[3]Treatments given as determined at the last follow-up.
DS, Durie–Salmon; ISS, International Staging System; VAD, vincristine, adriamycin and dexamethasone; HDT, High-dose therapy; HSCT, haematopoietic stem cell transplantation.

52.5% vs. 29.7%, $P = 0.004$) and ISS stage III (76.9% vs. 53.5% $P = 0.019$) (Table 1). In addition, they showed a trend of a lower proportion of IgA immunophenotype (17.5% vs. 30.7%, $P = 0.085$). In terms of induction chemotherapy, a difference was not found in the proportion of patients who received high-dose dexamethasone-containing regimens. At the last follow-up, a significantly lower proportion of patients with pre-existing diabetes had received bisphosphonate therapy (65% vs. 81.1%, $P = 0.019$) (Table 1).

Antidiabetic therapy and glycaemic control in MM patients with pre-existing diabetes

Glycaemic control and related events after the diagnosis of myeloma could be evaluated in 34 patients. At diagnosis of MM, diabetes had been diagnosed at a median period of 10 yr earlier (range 0.3–40), and 30 patients (82.4%) had received oral antidiabetic agents as glycaemic control (Table 2), with median and mean values of HbA1C 6.7% (range 5.3–12.1) and 7.12%, respectively. Complications related to diabetes were found in 6 (17.6%) of these patients, including neuropathy ($n = 5$), nephropathy ($n = 3$) and retinopathy ($n = 2$). RI was present at the diagnosis of myeloma in two of three of these patients with diabetes-related nephropathy. In addition, one patient who did not have diabetic nephropathy before diagnosis received renal biopsy for acute kidney injury at diagnosis of myeloma. The pathological findings confirmed cast nephropathy.

In the 34 evaluable patients, antidiabetic therapy was changed in 10 (29.4%) following the diagnosis of MM; all ten of these patients had received oral antidiabetic agents before the diagnosis of MM. Of these ten patients, antidiabetic therapy was changed to insulin in eight patients and two did not receive oral antidiabetic agents or insulin. Hyperglycaemia, as an adverse reaction to antidiabetic treatments, was noted in 23 patients (67.6%), including grades 2, 3 and 4 in 11 (32.3%), 9 (26.5%) and 3 (8.8%) patients, respectively. Antimyeloma regimens containing high-dose dexamethasone were found in ten of 12 patients with hyperglycaemia of grades 3 and 4 compared with three of 11 patients with grade 2 hyperglycaemia ($P = 0.012$). Hypoglycaemia was noted in six patients (17.6%), including grades 1 and 4 in 5 (14.7%) and 1 (2.9%) patients, respectively. High-dose dexamethasone-containing regimens had been administered in three of these six patients.

Table 2 Glycaemic control and related events in 34 evaluable patients with MM and pre-existing diabetes

Glycaemic control	No. (%)
Before	
Diet	4 (11.7)
Oral antidiabetic agents	28 (82.4)
Insulin	2 (5.9)
After	
Diet	6 (18.6)
Oral antidiabetic agents	18 (52.9)
Insulin	10 (29.4)
Adverse events related to glycaemic control	
Hyperglycaemia	23 (67.6)
Hypoglycaemia	6 (17.6)

Renal impairment and its reversal in patients with MM in relation to pre-existing diabetes

Given the higher proportion of RI (SCr $\geq$ 2.0 mg/dL) in patients with pre-existing diabetes at diagnosis of MM (Table 1), the baseline renal functions were rated using several scales. This revealed significantly higher levels of SCr and eGFR and a higher proportion of CKD stage 4 and 5 in these patients (Table 3). Furthermore, because patients with pre-existing diabetes might have had irreversible kidney disorders that led to the higher RI rate at diagnosis of myeloma, the rate of RI reversal was examined and compared. For all patients with MM, the rate of RI reversal was inversely correlated with the levels of SCr at diagnosis, with rates of 55.6%, 47.5% and 36.2% in patients with SCr $\geq$1.5, 2.0 and 3.0 mg/dL, respectively (Table 3). When patients with SCr $\geq$ 1.5 mg/dL at diagnosis were enrolled, MM patients with pre-existing diabetes showed a lower rate of RI reversal trend compared with their non-diabetic counterparts (40% vs. 58.8%, $P = 0.087$; Table 3).

Overall survival and prognostic factors of patients with MM in terms of pre-existing diabetes

The median OS of all patients was 21.6 months (95% CI = 16.2–26.9) and those with pre-existing diabetes had a significantly lower OS [with vs. without = 11.7 vs. 22.4 months; $P = 0.037$; hazard ratio (HR) = 1.509; 95% CI = 1.023–2.225] (Fig. 1 and Table 4). In addition to pre-existing diabetes, univariate analysis revealed that several factors were associated with a lower OS in all patients at diagnosis including old age ($\geq$65 yr), anaemia, hypoalbuminaemia, hypercalcaemia, RI, elevated serum β_2 microglobulin ($S\beta_2M \geq 3.5$ mg/L), elevated serum LDH, DS stage III and ISS stage III (Table 4). In patients with RI at elevated SCr $\geq$ 1.5 mg/dL or $\geq$2.0 mg/dL, those patients who experienced RI reversal had a significantly higher OS. Using the factors mentioned previously at diagnosis (with the exception of DS, ISS and RI reversal), the following observation was made with the Cox proportion model: three factors at diagnosis, including elevated $S\beta_2$ M ($\geq$3.5 mg/L), hypercalcaemia and old age ($\geq$65 yr), were independently associated with a lower OS and had HRs of 1.984 ($P = 0.004$; 95% CI = 1.245–3.162), 1.687 ($P = 0.005$; 95% CI = 1.174–2.424) and 1.656 ($P = 0.004$; 95% CI = 1.177–2.328), respectively (Table 4). In this model, pre-existing

Table 3 Renal impairment and its reversal of patients with MM in relation to the presence of pre-existing diabetes

	Overall (%)	Pre-existing diabetes		*P* value
		No (%)	Yes (%)	
No. of patients	310 (100)	270 (100)	40 (100)	
Serum creatinine (mg/dL) median (range)	1.4 (0.1–17.8)	1.4 (0.1–17.8)	2.2 (0.7–10.5)	0.027[1]
eGFR median (range)	38.2 (2.1–168.7)	39.3 (2.1–168.7)	23.7 (3.9–94.1)	0.021[1]
CKD stage 4 and 5	116 of 309 (34.5)	93 of 269 (34.6)	23 (57.5)	0.005
RI reversal in patients with SCr (mg/dL) at				
≥ 1.5	85 of 153 (55.6)	75 of 128 (58.6)	10 of 25 (40.0)	0.087
≥ 2.0	48 of 101 (47.5)	41 of 80 (51.3)	7 of 21 (33.3)	0.143
≥ 3.0	25 of 69 (36.2)	21 of 53 (39.6)	4 of 16 (25.0)	0.286

[1]By Mann–Whitney test.
CKD, chronic kidney disease; RI, renal impairment; SCr, serum creatinine.

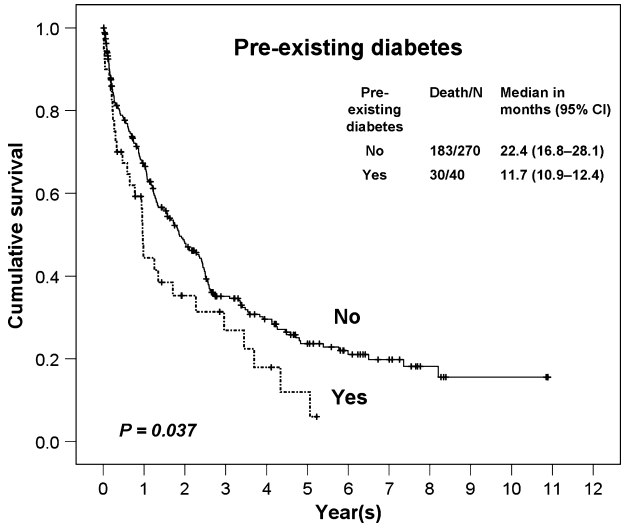

Figure 1 Overall survival curve of 310 patients with multiple myeloma in relation to pre-existing diabetes.

diabetes and RI at elevated SCr $\geq$ 2.0 mg/dL showed a lower OS trend (Table 4).

Discussion

To our knowledge, our study is the first to suggest that MM patients with pre-existing diabetes have an approximately 50% higher all-cause mortality compared with their non-diabetic counterparts. The hazards were presumably related to the significantly increased rate of RI and ISS stage III at diagnosis and a lower rate of RI reversal in these patients. The increase in all-cause mortality risk in our patients with MM (HR = 1.509) was similar to that recently reported in patients with breast cancer (HR = 1.49) (33). As described (33), the hazards of diabetes in patients with cancer may include adverse prognostic factors at diagnosis, less aggressive treatments, greater risks of treatment-related toxicities and a higher progression or relapse rate caused by underlying hyperinsulinaemia. We found that MM patients with pre-existing diabetes had at least two unfavourable factors at diagnosis, including higher rates of RI and elevated serum Sβ_2M ($\geq$5.5 mg/L, also categorized as ISS stage III). Several mechanisms are implied for this phenomenon. First, studies of myeloma-aggravating symptoms such as proteinuria and RI may be delayed in patients with pre-existing diabetes (12). Only one patient with MM who had pre-existing diabetes received renal biopsy at diagnosis of myeloma. Second, similar to the findings in solid tumours (33–35), pre-existing diabetes-related hyperglycaemia, insulin resistance and the resulting hyperinsulinaemia may stimulate the growth of myeloma cells. Sprynski *et al.* (36) suggested that insulin is a potent myeloma cell growth factor through insulin/insulin growth factor I (IGF-I) hybrid receptor activation. Third, pre-existing diabetes itself might not only aggravate the severity of RI at diagnosis of myeloma but may also limit the success of RI reversal in patients with MM. In Taiwan (37), United States (38) and Europe (39), type 2 diabetes is the most common cause of CKD (40) and accounts for 20–44% of patients with end-stage renal disease. In the analysis of renal biopsy in patients with monoclonal gammopathy, Pauekasakon *et al.* (41) found that diabetic nephropathy is the most common aetiology (18.1%) in those with unrelated renal diseases. Stratta *et al.* (42) recently found that type 2 diabetes is the strongest risk factor for progression of renal disease in older patients with monoclonal immunoglobulin deposition diseases including MM, with an HR of 3.65-fold. Furthermore, we found that MM patients with pre-existing diabetes showed a lower rate of RI reversal trend (Table 3). Similar to previous reports (43), we showed a favourable prognosis in patients with RI reversal (Table 4). Finally, the higher frequencies of RI at diagnosis and, subsequently, lower RI reversal rates and shorter OS (i.e. period of follow-up) might have limited further bisphosphonate administration in MM patients with pre-existing diabetes, although evidence for the survival benefit of these agents is hitherto rather weak.

Table 4 Prognostic factors of 310 patients with MM related to the presence of pre-existing diabetes

	Univariate			Multivariate		
Parameters	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Sβ_2 M $\geq$3.5 mg/L	3.081	2.059–4.61	<0.001	1.984	1.245–3.162	0.004
Serum total calcium (corrected) > 11.5 mg/dL	2.373	1.706–3.301	<0.001	1.687	1.174–2.424	0.005
Stage–ISS–III	2.258	1.694–3.011	<0.001	–	–	–
Serum creatinine $\geq$ 2.0 mg/dL	2.156	1.628–2.856	<0.001	1.368	0.983–1.904	0.063
Stage–DS–III	2.119	1.52–2.953	<0.001	–	–	–
Age $\geq$ 65	2.132	1.553–2.928	<0.001	1.656	1.177–2.328	0.004
Haemoglobulin < 10 g/dL	1.872	1.385–2.529	<0.001	1.112	0.782–1.582	0.555
Pre-existing diabetes	1.509	1.023–2.225	0.037	1.477	0.99–2.204	0.056
Serum albumin < 3.5 g/dL	1.405	1.068–1.848	0.015	1.082	0.809–1.448	0.594
Serum LDH > reference value	1.373	1.045–1.804	0.023	1.214	0.914–1.614	0.181
Gender–male vs. female	1.351	0.983–1.855	0.064	1.064	0.754–1.502	0.722
Platelets < 130 000/μL	1.257	0.945–1.673	0.116	–	–	–
WBC < 4000/μL	1.074	0.776–1.487	0.667	–	–	–
RI reversal–yes[1]	0.427	0.273–0.665	0.001	–	–	–
RI reversal–yes[2]	0.377	0.261–0.544	<0.001	–	–	–

[1]For patients with SCr $\geq$ 2.0 mg/dL.
[2]For patients with SCr $\geq$ 1.5 mg/dL.
–, the factors that were not enrolled in the multivariate analysis.
DS, Durie–Salmon; ISS, International Staging System; RI, renal impairment.

The trend of an RI-independent hazard on the OS in the Cox regression model (HR = 1.477; 95% CI = 0.99–2.20; $P = 0.056$) suggests that pre-existing diabetes is associated with other hazards, in addition to renal impact, in patients with MM. We found that more than 15% of MM patients with pre-existing diabetes had at least one hypoglycaemic event during treatment, and the method of glycaemic control had been changed in nearly one-third (29.4%) of patients, which might have further limited proper administration of antimyeloma treatment in these patients. Myeloma-derived insulin-like growth factors (IGF) may have had antidiabetic effects, thus participating in these events (44). Two patients in our study had RI at diagnosis of MM, and all antidiabetic agents were not administered after MM diagnosis.

On the other hand, the hazards of pre-existing diabetes on patients with MM should be carefully weighed against known prognostic factors (e.g. age and RI) and other comorbidities. Kleber *et al.* (7) recently analysed the hazards of several comorbidities including diabetes in 127 German patients and suggested that the poor OS was associated with the comorbidity and moderate to severe lung disease, rather than with diabetes. However, similar to the findings of our study, older age and RI were associated with a poor OS. In comparison with the patients studied by Kleber *et al.*(7), our patients were predominantly men (72.9% vs. 55%) because of the nature of our institution (i.e. a veteran's hospital), relatively older (median age, 71.8 vs. 60 yr), and had a lower $eGFR_{MDRD}$ (median, 38.2 vs. 88 mL/min/1.73/m^2) and ISS III (56.5% vs. 26%) at diagnosis. It is reasonable to speculate that pre-existing diabetes affects the prognosis of patients with MM, especially in the elderly and for those with RI at diagnosis of myeloma.

Our present study has several limitations. As described (21, 22), our patients were relatively older and included high proportions of patients with RI and ISS stage III at diagnosis. In addition, only 10% of patients had received HDT and HSCT. Therefore, the relatively lower OS may have led to the loss of the prognostic impact of hypoalbuminaemia in the multivariate analysis. Although the patients were unselected and the sample size was higher than those in most clinical trials related to MM (5, 6, 9), only 40 patients had pre-existing diabetes. Our study enrolled patients with pre-existing diabetes who received only diet control before myeloma diagnosis because steroid-containing antimyeloma treatment might increase insulin resistance. We used all-cause mortality as the primary endpoint rather than a myeloma-specific one because it was difficult to specify the cause of death. We were not able to conclude whether the prevalence of type 2 diabetes was higher in our patients with MM (12.9%) than in the control population because we were limited by the nature of the retrospective analysis. An analysis of the elderly population ($\geq$65 yr) in Taiwan estimated that the prevalence of type 2 diabetes was 16.9% in 2000 (45). Finally, no comprehensive studies have differentiated the source of RI and proteinuria from either diabetes or myeloma.

The numbers of MM patients with pre-existing diabetes are expected to increase because of the progressively ageing population. The findings of our study provide important clues that pre-existing diabetes has an impact on the renal and even survival outcome in patients with MM. After weighing the risk of peripheral neuropathy and venous thrombosis (8–12), the possibility of achieving RI reversal in MM patients with pre-existing diabetes using novel agents

cannot be overlooked. In addition, caution should be taken in these patients in terms of glycaemic control and accompanying adverse events after diagnosis of MM.

Disclosures

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