Poster #T-146

Newly Diagnosed Multiple Myeloma (NDMM): Effect of Age, Renal Insufficiency, and Cardiovascular Disease on Overall Survival and Treatment Patterns Among Stem Cell Transplant-ineligible Patients in the United States (US)

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Introduction and Background

- The introduction of proteasome inhibitors (PIs) and immunomodulators (IMIDs) into multiple myeloma (MM) treatment in the last decade has led to significant improvements in patients outcomes.[1]
- Comorbid renal insufficiency (RI) and cardiovascular (CV) disease often lead to shorter survival in myeloma, especially in the elderly patient population.[2,3]
- We describe United States (US) treatment patterns and outcomes in newly diagnosed multiple myeloma (NDMM) patients ineligible for stem cell transplant (SCT) treated with first-line therapy (1LT) in routine clinical practice adjusted to age and presence of renal and cardiovascular comorbidities.

Materials and Methods

Study Design

- This was a retrospective cohort study using Humedica, a large national electronic medical record database in the US.
- Adult patients (≥18 years of age) with NDMM who initiated 1LT between 1/1/2008 and 12/31/2015 were included in the analysis if they had evidence of at least 1 of the following CRAB symptoms: hypercalcemia, RI, anemia, or bone disease identified by International Classification of Diseases (ICD) diagnosis codes and/or laboratory values within 6 months prior to through 1 month post-index MM diagnosis date.
  - Bone disease was proxied by ICD codes for fracture, radiation, bone-directed surgery, and spinal cord compression.
  - Lab values used in definitions were as follows: renal insufficiency, creatinine clearance <40 mL/min or serum creatinine >2 mg/dL; hypercalcemia, corrected calcium >11 mg/dL; anemia, hemoglobin <10 gm/dL.
- Eligible patients had to have continuous care in an integrated delivery network medical facility for 12 months prior to the index diagnosis date (first claim with an MM diagnosis code [ICD-9 code: 203.0x; ICD-10 code: C90.0x]) through at least initiation of 1LT for NDMM.
- Patients with other primary cancers or evidence of metastatic disease prior to index MM diagnosis or those who underwent a front-line SCT were excluded.

Study Measures

- Comorbid RI was identified based on the presence of a diagnosis code or a lab value (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL) in the 6 months prior to index diagnosis date through 1 month post-index diagnosis date.
- Comorbid CV disease and Charlson comorbidity index (CCI) were derived from ICD diagnosis codes within 1 year pre-index diagnosis date.
- High-risk cytogenetics were defined as del[17p], t[4;14], t[14;16], and/or 1q21 gain.
- The time from the start of 1LT to initiation of second-line therapy (2LT), referred to as time to next treatment (TTNT), or death was used as a surrogate measure of progression-free survival (PFS).
  - 2LT was identified accordingly:
    - Re-treatment after a treatment gap of >3 months of 1LT or
    - Switch to another drug combination after starting 1LT

Study Analyses

- Kaplan-Meier analyses were performed to calculate duration of therapy (DOT) from the start of 1LT by comorbidity profile and age.
- Patients were censored at loss to follow-up or the end of study period (12/31/2015).
- The effects of comorbidity profile on overall survival (OS) and TTNT were assessed using Cox proportional hazards models adjusted for covariates.

Results

Patient Characteristics

- Among 2,070 patients, 41.6% were ≥75 years of age (n=861), and these patients had a higher mean CCI score than their younger counterparts aged <75 years (1.3 vs 1.1; *P*<0.01).
- The majority (56.3%) of patients had comorbid RI with or without comorbid CV disease.
  - A significantly higher proportion of the elderly suffered from RI (63.3% vs 51.4%; *P*<0.01) and CV disease (25.1% vs 18.4%; *P*<0.01) compared to younger patients at the time of initiation of 1LT.

Treatment Patterns

- PI-based 1LT was most common (>40%) regardless of age or presence of comorbidities. PI-based therapy predominated among patients with RI (51.8%) and those with concomitant RI and CV disease (48.2%). Patients with CV disease alone were equally likely to receive a PI-based or an IMID-based regimen (35.2% in both groups) (**Table 2**).
- Elderly patients (aged ≥75 years) were less likely to receive intensive therapy with a ≥3-drug regimen in 1LT (21.6% vs 36.8%), including an IMID+PI combination in 1LT (12.5% vs 20.3%) than younger patients (aged <75 years).

Duration of Therapy

- Overall, the median DOT was 5.9 months (95% confidence interval [CI]: 5.5, 6.2) with 1LT (**Table 3**).
  - DOT did not differ based on age (*P*=0.46).
  - A significant variation in DOT by comorbidity status was observed (*P*<0.01).

Outcomes: Time to Next Treatment and Overall Survival

Univariate Analysis

- Overall, the median TTNT was 16.1 months (95% CI: 15.1, 17.2) from initiation of 1LT, and the median OS from initiation of 1LT was 44.8 months (95% CI: 40.3, 49.0).
- There was significant variation in both TTNT and OS by age and comorbidity status (**Table 4**).

Multivariate Analysis

- After adjusting for race, ethnicity, gender, stage, cytogenetic risk, type of 1LT (PI, IMID, PI/IMID, other), diabetes, thromboembolic disease, geographic region, and year of diagnosis:
  - Age ≥75 years was associated with a significantly shorter TTNT and OS (**Figure 1, Panel A and Figure 2, Panel A**).
  - Comorbid CV disease, RI, or RI plus CV disease was not associated with TTNT (**Figure 1, Panel B**).
  - However, patients with RI with or without comorbid CV disease had worse OS, while comorbid CV disease alone was not a negative prognostic factor for OS (**Figure 2, Panel B**).

Table 1. Baseline Characteristics

Variable		Overall	Age		*P*-value
			<75 years N=1,209	≥75 years N=861	
Overall, N		2,070	1,209	861	
Gender (%)	Male	51.3	52.4	49.7	0.22
Race (%)	African American	19.6	21.6	16.8	<0.01
	Caucasian	72.8	68.9	78.3	
	Asian/other/unknown	7.6	9.5	4.9	
Ethnicity (%)	Hispanic	3.4	4.6	1.7	<0.01
	Not Hispanic	85.8	85.0	87.0	
	Unknown	10.8	10.4	11.3	
Region (%)	Midwest	50.5	47.4	54.8	<0.01
	Northeast	11.4	11.0	12.0	
	South	30.3	34.1	25.0	
	West/other/unknown	7.8	7.5	4.2	
Cytogenetics (%)	High-risk	10.5	12.5	7.8	<0.01
	Not high-risk	0.9	1.0	0.7	
	Unknown	88.6	86.5	91.5	
ISS stage	Stage I	3.2	3.3	3.0	0.20
	Stage II	5.0	4.3	5.9	
	Stage III	4.4	4.0	5.1	
	Unknown	87.4	88.4	86.0	
CCI[a] mean (SD)		1.2 (1.6)	1.1 (1.6)	1.3 (1.6)	<0.01
Comorbidities[a] (%)	Thromboembolic disease	9.6	7.4	12.5	<0.01
	Diabetes	21.0	20.4	22.0	0.38
CRAB symptoms present[a] (%)	RI without CV disease	42.0	40.0	44.7	<0.01
	CV disease without RI	6.7	7.1	6.5	
	Both RI and CV disease	14.3	11.3	18.6	
Time from index diagnosis to end of follow-up, mean months (SD)		25.3 (19.2)	27.0 (19.9)	22.9 (17.9)	<0.01
Time from index diagnosis date to start of 1LT, mean months (SD)		4.5 (9.2)	4.6 (9.6)	4.4 (8.6)	0.49

[a] CCI scores and baseline comorbidities are relative to the 12 months preceding index diagnosis date.
Key: 1LT – first-line therapy; CCI – Charlson comorbidity index; CV – cardiovascular; ISS – International Staging System; RI – renal insufficiency; SD – standard deviation.

Table 2. Regimen Type by Age

Population, %		Overall N=2,070	By Age		By Comorbidity			
			Age <75 years N=1,209	Age ≥75 years N=861	No RI or CV disease N=762	RI only N=869	CV disease only N=142	RI and CV disease N=297
Combination therapy	≤2-drug combination	69.5	63.2	78.4	68.9	69.5	73.9	69.0
	≥3-drug combination	30.5	36.8	21.6	31.1	30.5	26.1	31.0
Therapeutic class	PI-based	45.8	49.9	40.1	40.0	51.8	35.2	48.2
	IMID-based	27.6	22.4	35.0	31.1	23.8	35.2	26.3
	PI + IMID-based	17.1	20.3	12.5	18.8	15.7	16.9	16.8
	Other[a] (not categorized elsewhere)	9.5	7.4	12.4	10.1	8.8	12.7	8.8

[a] Other included bendamustine, cisplatin, cyclophosphamide, doxorubicin, melphalan, etoposide, vorinostat, or vincristine.
Key: CV – cardiovascular; IMID – immunomodulator (lenalidomide, thalidomide, or pomalidomide); PI – proteasome inhibitor (bortezomib or carfilzomib); RI – renal insufficiency.

Table 3. Duration of Therapy by Subgroup

Regimen Type		Duration of Therapy		
		Median, months	95% CI	*P*-value
Overall		5.9	5.5, 6.2	–
By age	Age <75 years (n=1,209)	5.9	5.5, 6.3	0.46
	Age ≥75 years (n=861)	5.9	5.3, 6.7	
By comorbidity	No RI nor CV disease (n=762)	6.1	5.6, 6.8	<0.01
	RI only (n=869)	5.8	5.3, 6.3	
	CV disease only (n=142)	7.1	5.5, 10.2	
	Both RI + CV disease (n=297)	5.1	4.4, 6.1	

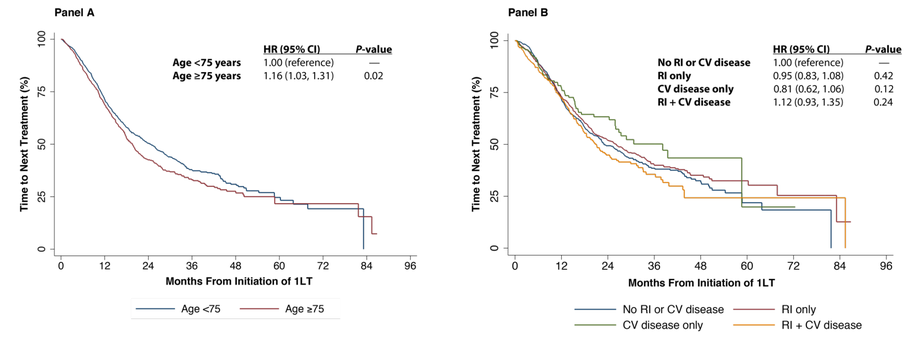
Key: CI – confidence interval; CV – cardiovascular; RI – renal insufficiency.

Table 4. Univariate Analysis of TTNT and OS by Age and Comorbidity Status

Subgroup Analysis		TTNT		OS	
		Median, months (95% CI)	*P*-value	Median, months (95% CI)	*P*-value
Overall		16.1 (15.1, 17.2)	N/A	44.8 (40.3, 49.0)	N/A
By age	Age <75 years (n=1,209)	17.0 (15.5, 18.5)	0.01	55.6 (50.6, 67.8)	<0.01
	Age ≥75 years (n=861)	15.1 (13.9, 16.8)		28.9 (25.7, 32.9)	
By comorbidity	No RI nor CV disease (n=762)	15.9 (13.9, 17.7)	0.03	51.0 (47.3, 58.7)	<0.01
	RI only (n=869)	16.3 (15.0, 17.9)		41.4 (34.7, 48.7)	
	CV disease only (n=142)	24.3 (15.5, 30.7)		46.6 (34.9, NE)	
	Both RI + CV disease (n=297)	14.9 (13.1, 17.2)		29.9 (21.1, 37.3)	

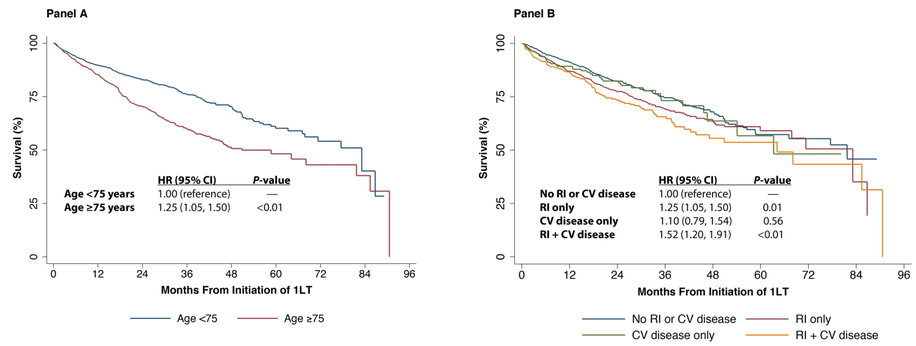
Key: CI – confidence interval; CV – cardiovascular; OS – overall survival; RI – renal insufficiency; TTNT – time to next treatment.

Figure 1. Predicted TTNT Based on Age[a] (Panel A) and Comorbidities[b] (Panel B)



[a] Adjusted for presence of RI/CV disease, race, ethnicity, gender, stage, cytogenetic risk, type of 1LT (PI, IMID, PI/IMID, other), diabetes, thromboembolic disease, region, year of diagnosis.
[b] Adjusted for age (<75, ≥75), race, ethnicity, gender, stage, cytogenetic risk, type of 1LT (PI, IMID, PI/IMID, other), diabetes, thromboembolic disease, region, year of diagnosis.
Key: 1LT – first-line therapy; CI – confidence interval; CV – cardiovascular; HR – hazard ratio; IMID – immunomodulator (lenalidomide, thalidomide, or pomalidomide); PI – proteasome inhibitor (bortezomib or carfilzomib); RI – renal insufficiency; TTNT – time to next treatment.

Figure 2. Predicted OS Based on Age[a] (Panel A) and Comorbidities[b] (Panel B)



[a] Adjusted for presence of RI/CV disease, race, ethnicity, gender, stage, cytogenetic risk, type of 1LT (PI, IMID, PI/IMID, other), diabetes, thromboembolic disease, region, year of diagnosis.
[b] Adjusted for age (<75, ≥75), race, ethnicity, gender, stage, cytogenetic risk, type of 1LT (PI, IMID, PI/IMID, other), diabetes, thromboembolic disease, region, year of diagnosis.
Key: 1LT – first-line therapy; CI – confidence interval; CV – cardiovascular; HR – hazard ratio; IMID – immunomodulator (lenalidomide, thalidomide, or pomalidomide); PI – proteasome inhibitor (bortezomib or carfilzomib); RI – renal insufficiency; TTNT – time to next treatment.

Limitations

- Limitations of this study include those inherent of any retrospective study. It is possible that some comorbidities were not captured through use of ICD-9 codes, and measures of frailty and performance status were not captured, which may confound outcomes.
- Also, cytogenetic abnormalities and ISS stage were not available for a majority of patients.

Conclusions

- Despite the introduction of PIs and IMIDs into US clinical practice, the median OS remained only 44.8 months in NDMM patients ineligible for stem-cell transplant treated between 2008 and 2015.
- The comorbidity burden was high in this cohort of NDMM patients, with the majority of patients (56.3%) presenting with RI and CV disease or RI alone at time of diagnosis of MM.
- Duration of therapy was shorter overall and in every subgroup than time to next treatment (the surrogate for PFS).
- Both older age ≥75 years and RI ± CV disease conferred worse OS despite more frequently used novel agents (PI and/or IMID, 90.5%) in this study.
  - Regimens containing ≤2 agents were the most frequently used 1LT in this NDMM patient population ineligible for stem-cell transplant.
- New efficacious and safe therapies for the elderly NDMM population are needed.

References

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3. Yong C, Seal B, Farrelly E, et al. Practice patterns and outcomes in US patients with relapsed/refractory multiple myeloma (RRMM) and comorbid renal dysfunction and/or cardiovascular disease. Poster presented at the 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

Disclosures

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