Poster #F-209

Predictors of Treatment With Triplet First-line Therapy Among Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (NDMM) in Routine Clinical Care

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Introduction and Background

- Triplet therapy with immunomodulators (IMIDs) and proteasome inhibitors (PIs) is an increasingly accepted strategy to optimize outcomes in newly diagnosed multiple myeloma (NDMM).
- European guidelines indicate that in patients not eligible for stem cell transplant, treatment with a triplet regimen is warranted and recommend a novel agent in combination with melphalan.[1,2]
- The most recent update of the National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (MM) indicate that a triplet regimen should be used as standard therapy for NDMM patients; however, elderly or frail patients may be treated with doublet regimens.[3]
  - Further, they have deprioritized melphalan-based regimens in favor of novel agents.
- The use of triplet first-line therapy, however, in routine care has not been systematically examined.
- We assessed adoption of and factors influencing treatment choice with triplet first-line therapy in a United States (US) cohort of NDMM patients.

Materials and Methods

Study Design

- This was a retrospective cohort study using Humedica, a large national electronic medical record database in the US.
- Inclusion criteria:
  - Adult (≥18 years of age) NDMM patients with evidence of starting first-line MM-specific anticancer therapy (per NCCN MM guidelines, version 3.2017[3]) between 1/1/2008 and 12/31/2015.
  - Evidence of at least 1 of the following CRAB symptoms: hypercalcemia, renal insufficiency, 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.
  - 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.
- Exclusion criteria:
  - Front-line stem-cell transplant
  - Other malignancy prior to index MM diagnosis
- Follow-up ended upon the earliest of the following: death, loss to follow-up, or end of study.

Study Measures

- Induction first-line therapy was categorized accordingly:
  - PI-based: bortezomib or carfilzomib ± any non-IMID
  - IMID-based: lenalidomide, thalidomide, or pomalidomide ± any non-PI
  - PI + IMID-based: any PI + any IMID ± any other MM-specific agent
  - Other: dexamethasone monotherapy >90 days, bendamustine, cisplatin, cyclophosphamide, doxorubicin, melphalan, etoposide, vorinostat, or vincristine
- Triplet therapy included any ≥3-drug combination regimen; non-triplet therapy included any ≤2-drug combination regimen.
- Charlson comorbidity index (CCI) and the presence of cardiovascular disease 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. A natural language processing algorithm was used to identify cytogenetic results in free text in the electronic medical record.

Study Analyses

- Rates of triplet therapy use over time (ie, year of start of triplet therapy) were captured, and changes in these rates over time were evaluated with the Cochran-Armitage trend test.
- Stepwise multiple logistic regression was used to estimate predictors of triplet therapy use. Variables that were tested as potential predictors included age, gender, race, year of diagnosis, anemia, bone disease, renal insufficiency, hypercalcemia, geographic region, college education, income, cytogenetic risk, cardiovascular disease, CCI, and International Staging System (ISS) stage.
- All statistical tests were 2-tailed; *P*-value <0.05 was defined as significant.

Results

Patient Characteristics

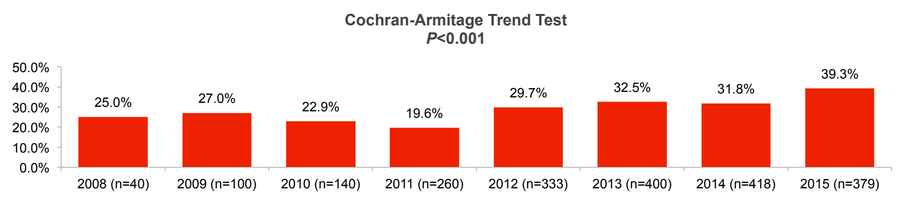
- Among 2,070 NDMM patients not undergoing front-line stem cell transplant, 631 patients (30.4%) initiated therapy with a ≥3-drug regimen and 1,439 patients (69.6%) initiated therapy with a ≤2-drug regimen.
- The triplet therapy group was younger (mean age: 67.3 vs 71.3 years) and more likely to have known high-risk cytogenetics (15.9% vs 8.2%), hypercalcemia (27.6% vs 22.2%), and bone disease (38.0% vs 30.7%) than the non-triplet therapy group (*P*<0.01, for all) (**Table 1**).
- However, both groups had a similar CCI score (mean: 1.2 for each).
- The use of triplet therapy increased significantly over the study period (*P*<0.01), with 25% in 2008 and 39.3% in 2015 (**Figure 1**).

Table 1. Baseline Characteristics

Variable		Overall	Age		*P*-value
			<75 years	≥75 years	
Overall, N		2,070	1,209	861	0.19
Gender (%)	Male	51.3	634 (52.4)	427 (49.6)	0.79
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.	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	34.2	25.0	
	West/other/unknown	7.8	7.4	8.2	
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] (%)	Cardiovascular disease	21.2	18.4	25.1	<0.01
	Thromboembolic disease	9.6	7.4	12.5	<0.01
	Diabetes	21.0	20.3	22.0	0.38
CRAB symptoms present[a] (%)	Renal insufficiency	56.3	51.4	63.3	<0.01
	Anemia	84.6	84.4	84.8	0.84
	Hypercalcemia	23.8	25.1	22.0	0.09
	Bone disease	32.9	35.6	29.0	<0.01
Time from index diagnosis to end of follow-up, mean months (SD)		25.3 (19.2)	27 (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.
[b] CRAB symptoms are relative to the 6-month period preceding index diagnosis date up to 1-month post-index diagnosis date.
Key: 1LT – first-line therapy; CCI – Charlson comorbidity index; CRAB – hypercalcemia, renal insufficiency, anemia, or bone disease; ISS – International Staging System; SD – standard deviation.

Figure 1. Proportion of Patients With NDMM Initiating First-line Therapy by Year



Key: NDMM – newly diagnosed multiple myeloma.

Regimen Type for Patients Receiving First-line Triplet Therapy

- Among the 631 patients who initiated triplet therapy, the majority (n=316; 50.1%) received therapy with a PI + a cytotoxic or vorinostat ± a steroid (**Table 2**).
  - 90.5% (n=286) of these patients were treated with bortezomib + a steroid + either the alkylators cyclophosphamide or melphalan or with doxorubicin.
- A PI + IMID combined with either a steroid or with a traditional cytotoxic agent(s) or vorinostat ± a steroid made up another 44.6% (n=281).
  - Of these 281 patients, (70.5%) received lenalidomide + bortezomib + a steroid.
- In 1,439 patients (69.5% of the overall population) with non-triplet therapy, the majority of regimens were:
  - PI ± other (43.9%; largely bortezomib ± dexamethasone)
  - IMID ± other (38.4%, largely lenalidomide ± dexamethasone)
  - Other MM-specific therapy (12.7%)

Table 2. Types of First-line Triplet Regimens Among the 631 NDMM Patients Receiving ≥3-drug Combination

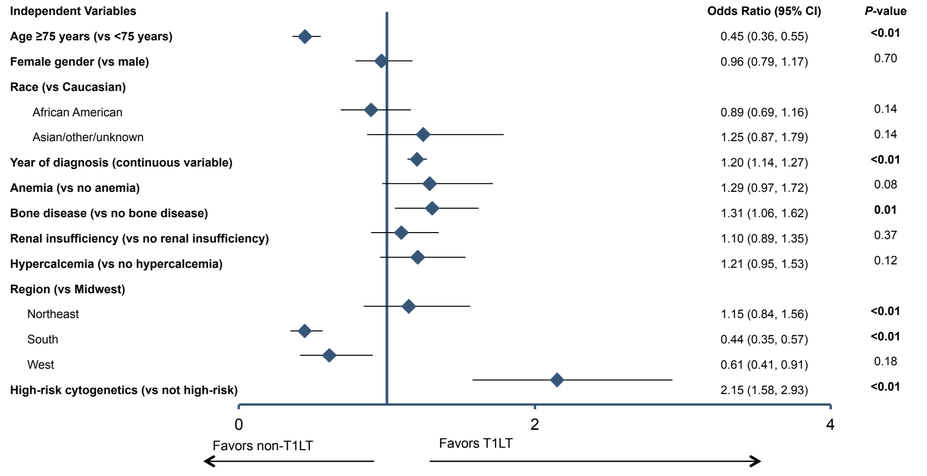
Regimen Type	N	Percent
PI + other[a] ± steroid	316	50.1
IMID + PI + steroid	225	35.7
IMID + PI + other[a] ± steroid	56	8.9
IMID + other[a] ± steroid	19	3.0
Other[a] triplet combination (not containing a PI nor IMID)	15	2.4

[a] Other included bendamustine, cisplatin, cyclophosphamide, doxorubicin, melphalan, etoposide, vorinostat, or vincristine.
Key: IMID – immunomodulator; PI – proteasome inhibitor.

Predictors of Triplet Therapy in First-line Therapy

- Stepwise multiple logistic regression analyses assessing the predictors of triplet first-line therapy revealed:
  - Older age (≥75 years) was associated with a decreased odds of triplet therapy being utilized vs those patients <75 years of age (odds ratio [OR]: 0.45; 95% confidence interval [CI]: 0.36, 0.55; *P*<0.01) (**Figure 2**).
  - Presence of high-risk cytogenetics was associated with higher odds of triplet therapy use (OR: 2.15 [95% CI: 1.58, 2.93], respectively; *P*<0.01).
  - A significant geographic variation was noted, with a lower likelihood of triplet therapy use in the Southern (OR: 0.44 [95% CI: 0.35, 0.57]) and Western regions (OR: 0.61 [95% CI: 0.41, 0.57]) but not the Northeastern (OR: 1.15 [95% CI: 0.84, 1.56]) compared to the Midwest regions.
- None of the following were independently associated with receipt of triplet therapy: CCI score, ISS stage of disease, nor pre-existing cardiovascular disease.

Figure 2. Predictors of First-line Triplet Therapy Use



Key: HCM – hypercalcemia; non-T1LT – use of ≤2-drug regimen in first-line treatment; RI – renal insufficiency; T1LT – triplet first line therapy (ie, ≥3-drug combination)

Limitations

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

Conclusions

- In this NDMM cohort, use of first-line triplet therapy increased in most recent years, perhaps due to evolving evidence supporting the superiority of triplets in induction therapy of transplant-ineligible NDMM patients.
  - However, most patients still did not receive triplet therapy in routine care.
- Age ≥75 years, known high-risk cytogenetics, and geographic region but not comorbidity status influenced treatment choice with triplet therapy.
- Given the recommendations for triplet therapy in patients able to tolerate such regimens,[1-3] barriers to triplet therapy utilization should be further examined.

References

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Disclosures

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