Real-World Study of Treatment Patterns in Heavily Pretreated Relapsed/Refractory Multiple Myeloma in the US

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Introduction

- The relapsed/refractory multiple myeloma (RRMM) treatment landscape is continuously evolving with many treatment regimens available as double- and triple-drug combinations[1]
- These regimens aim to control symptoms, delay progression, minimize adverse events, and ultimately prolong survival[2]
- Despite substantial improvements in clinical outcomes since the introduction of proteasome inhibitors (PI), immunomodulatory agents, and monoclonal antibodies (mAbs)[3], most patients with MM eventually relapse and/or become refractory to treatment[1]
- The choice of therapy offered to patients is influenced by its expected efficacy/tolerability, response to previous therapy, prior lines of therapy (LOT), and patient and disease characteristics[1]
- Currently, real-world evidence (RWE) on treatment patterns and outcomes in RRMM are limited, especially among those who have developed resistance to multiple classes of therapies
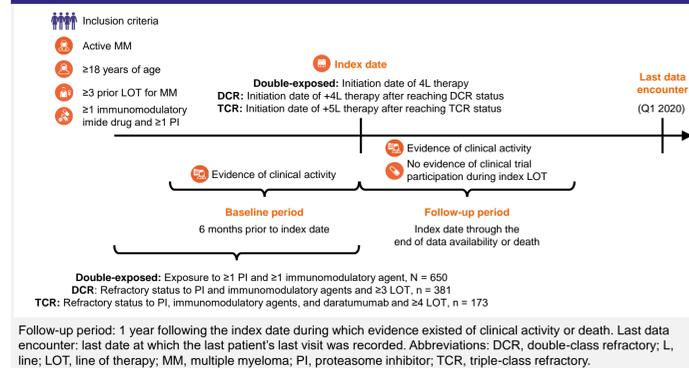
Objective

- To assess clinical treatment patterns and refractory status in heavily pretreated patients with RRMM

Methods

- This longitudinal retrospective cohort study utilized the COTA Healthcare de-identified real-world database derived from US electronic health records of partnered healthcare providers from Q3 1988 through Q1 2020
- Study design details and inclusion/exclusion criteria are presented in **Figure 1**
- Patients ≥18 years of age at index date with active RRMM previously exposed to ≥1 PI and ≥1 immunomodulatory agent (double-exposed) and who received ≥3 prior LOTs were included
- Refractory myeloma was defined as disease non-responsive to therapy within 60 days of last therapy
- In total, 650 of patients who met inclusion criteria were identified as double-exposed, which were further categorized into:
  – double-class refractory (DCR) n = 465 (72%) and triple-class refractory (TCR) n = 221 (34%)
  – further exclusions of patients younger than 18 years of age, without evidence of clinical activity or who participated in a clinical trial resulted in DCR n = 381 and TCR n = 173
- Assessments included therapies received before and during the index LOT, duration of treatment, and treatment discontinuation reasons. Index LOT began on the index date

Figure 1. Study design scheme

Follow-up period: 1 year following the index date during which evidence existed of clinical activity or death. Last data encounter: last date at which the last patient's last visit was recorded. Abbreviations: DCR, double-class refractory; L, line; LOT, line of therapy; MM, multiple myeloma; PI, proteasome inhibitor; TCR, triple-class refractory.

Results

Patient characteristics

- A summary of patient and disease characteristics are presented in **Table 1**
- Median number of prior LOTs was 3 for DCR patients and 6 for TCR patients

Table 1. Patient demographics and disease characteristics

Characteristic	Double-exposed to PI and immunomodulatory agents N = 650	Double-class refractory to PI and immunomodulatory agents N = 381	Triple-class refractory to PI, immunomodulatory agents, and anti-CD38 mAb n = 173
Age at index date, years			
Median (IQR)	65.2 (57.2, 72.8)	65.0 (57.6, 72.8)	65.5 (59.9, 73.7)
Sex, n (%)			
Male	348 (53.5)	213 (55.9)	86 (49.7)
Time from initial MM diagnosis to index, months			
Median (IQR)	36.4 (23.2, 57.2)	40.8 (25.5, 66.0)	61.6 (40.1, 86.1)
Follow-up time, months			
Median (IQR)	24.0 (10.5, 42.2)	14.3 (5.3, 29.2)	8.1 (3.3, 14.9)
Previous SCT, n (%)			
Autologous SCT	402 (61.8)	237 (62.2)	120 (69.4)
Allogeneic SCT	23 (3.5)	16 (4.2)	12 (6.9)
ISS disease stage, n (%)			
Stage I	114 (17.5)	78 (20.5)	50 (28.9)
Stage II	87 (13.4)	59 (15.5)	35 (20.2)
Stage III	68 (10.5)	53 (13.9)	27 (15.6)
Unknown	381 (58.6)	191 (50.1)	61 (35.3)
Cytogenetic abnormalities, n (%)			
Standard-risk cytogenetics	233 (35.8)	145 (38.1)	65 (37.6)
High-risk cytogenetics	314 (48.3)	212 (55.6)	114 (65.9)

Abbreviations: IQR, interquartile range; ISS, International Staging System; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; SCT, stem cell transplant.

Treatment patterns

- In all patient groups, PI/immunomodulatory agent-based therapy and daratumumab-based therapies were commonly received during index LOT and 2 subsequent therapies (**Figure 2**)
- In total, 23% of double-exposed, 30% of DCR, and 42% of TCR patients had no subsequent therapy after index LOT
- TCR patients were also most likely to receive investigational agents during first subsequent line after index LOT (11% TCR patients vs 8% of double-exposed vs 5% of DCR patients) and bortezomib-based therapies in the following LOTs
- In total, over 95% of patients received bortezomib (a PI) and lenalidomide (an immunomodulatory agent) prior to index LOT
- All TCR patients received daratumumab (anti-CD38 mAb), which was also administered to 65% of double-exposed and 75% of DCR patients
- TCR patients were more likely to receive carfilzomib and pomalidomide prior to index LOT compared with other cohorts

Discontinuations

- Reasons for treatment discontinuation during index LOT are shown in **Table 2**

Figure 2. Therapies received by patients in index LOT and 2 subsequent LOTs according to refractory status

A. Double-exposed patients (N = 650)

B. Double-class refractory patients (n = 381)

C. Triple-class refractory patients (n = 173)

Abbreviations: LOT, line of therapy; PI, proteasome inhibitor; SCT, stem cell transplant; TTNT, time to next treatment.
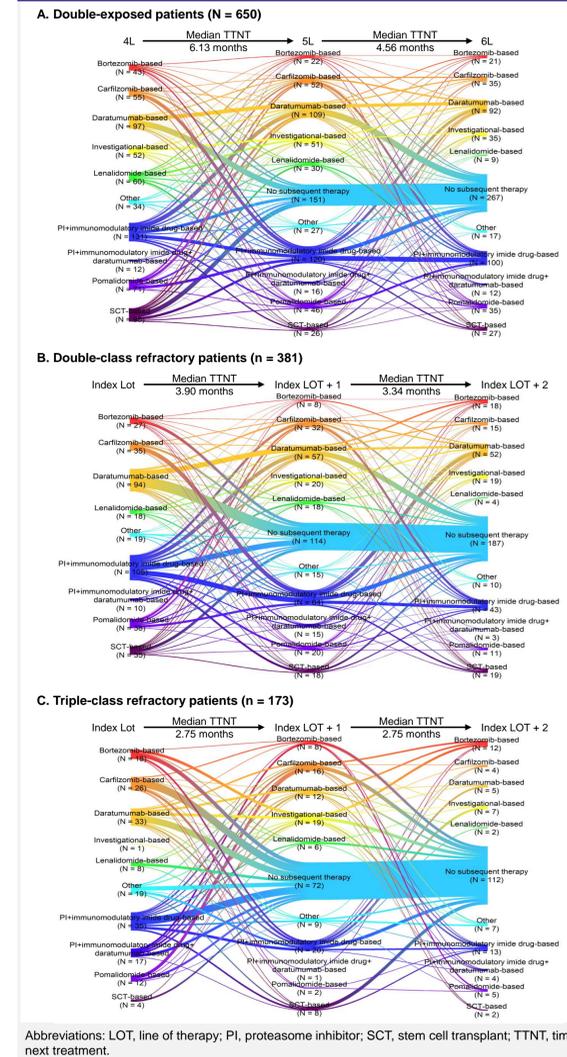
Table 2. Treatment discontinuations during index LOT

Reasons for treatment discontinuation	Double-exposed N = 650	Double-class refractory N = 381	Triple-class refractory n = 173
Discontinued, n (%)	483 (74.3)	296 (77.7)	125 (72.3)
Reason, n (%)			
Progression	290 (60.0)	176 (59.5)	75 (60.0)
Toxicity	137 (28.4)	68 (23.0)	31 (24.8)
Doctor preference	64 (13.3)	42 (14.2)	13 (10.4)
Inadequate response	32 (6.6)	16 (5.4)	5 (4.0)
Patient preference	16 (3.3)	8 (2.7)	2 (1.6)
Death	11 (2.3)	18 (6.1)	11 (8.8)
Unknown	10 (2.1)	10 (3.4)	3 (2.4)
Insurance reason	1 (0.2)	1 (0.3)	1 (0.8)

Abbreviations: LOT, line of therapy.

Time to refractory status

- Patients treated with lenalidomide and bortezomib had the longest median time to refractory status in all 3 refractory groups
  – Lenalidomide – double-exposed patients: median of 14.2 (interquartile range [IQR] 3.8, 36.3) months, DCR patients: 13.3 (3.8, 35.5) months, and TCR patients: 15.7 (5.0, 33.2) months
  – Bortezomib – double-exposed patients: median of 8.2 (2.9, 32.4) months, DCR patients: 9.0 (3.0, 34.5) months, and TCR patients 9.5 (3.0, 36.0) months
- Double-exposed patients had the shortest median time to refractory status after treatment with ixazomib and pomalidomide (3.7 [2.1, 6.9] and 3.7 [1.8, 10.0] months, respectively)
- The shortest time to refractory status among DCR and TCR patients was seen with thalidomide treatment (2.9 [1.3, 12.3] months and 2.4 [1.4, 8.8] months, respectively)
- TCR patients became refractory to daratumumab in a median of 3.7 months

Retreatment

- Bortezomib and lenalidomide had the highest retreatment rates among patients in all groups (**Figure 3**)

Figure 3. Rates of retreatment among patients previously treated with PIs, immunomodulatory agents, and daratumumab
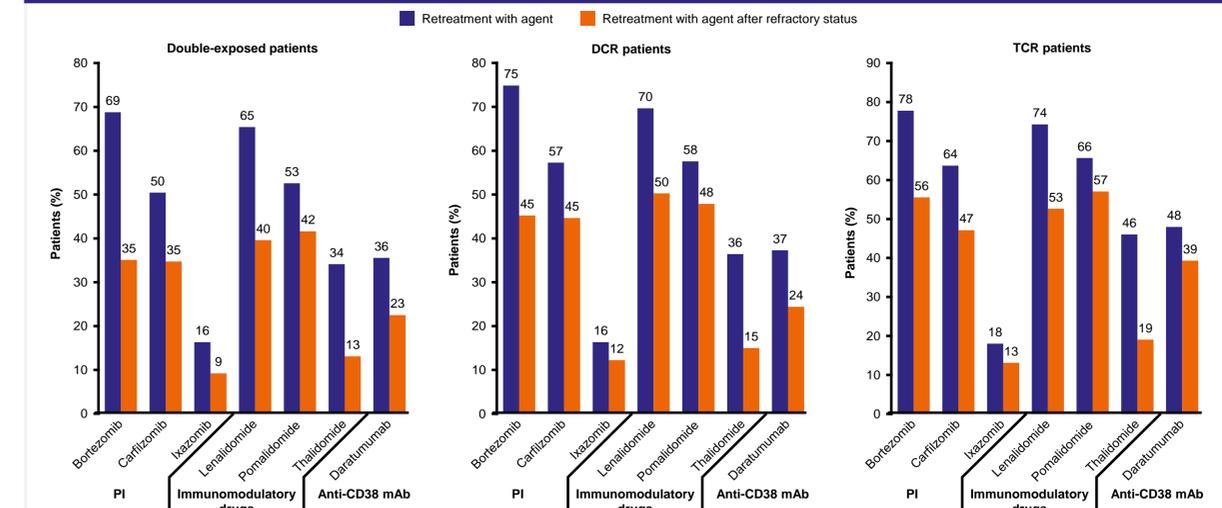
Abbreviations: DCR, double-class refractory; mAb, monoclonal antibody; PI, proteasome inhibitor; TCR, triple-class refractory.

Conclusions

- Analysis of RWE demonstrated that heavily pretreated TCR patients with RRMM have limited treatment options as evidenced by high rates of retreatment with PIs, immunomodulatory agents, and daratumumab and the reliance on investigational agents for patients with TCR disease
- Majority of patients discontinued their index therapy, mainly due to disease progression

Abbreviations

DCR, double-class refractory; IQR, interquartile range; ISS, International Staging System; LOT, line of therapy; mAbs, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; RWE, real world evidence; SCT, stem cell transplant; TCR, triple-class refractory; TTNT, time to next treatment.

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