PCN5

Assessment of Dose per Cycle of Dexamethasone in Lenalidomide–Dexamethasone Regimen to Treat Relapsed/Refractory Multiple Myeloma Patients in the United States

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Introduction

- Multiple myeloma (MM) consists of a heterogeneous group of neoplasms of plasma cells with variations in morphology, phenotype, molecular biology and clinical behavior[1]
- Estimates suggest that 30,280 new cases of myeloma will be diagnosed in the United States in 2017 (representing 1.8% of all cancers) and that 12,590 deaths during the year will be attributable to this malignancy (representing 2% of all deaths attributable to cancer)[2]
- Advances in autologous stem cell transplantation (ASCT) and the introduction of immunomodulatory drugs (IMiDs; eg, lenalidomide and pomalidomide) and proteasome inhibitors (PIs; eg, bortezomib and carfilzomib) have contributed to better response rates and significantly improved 5-year survival rates, which have increased by 74% between 1989 and 2010[3,4]
- Combination therapy is frequently employed to treat relapsed/refractory MM (RRMM), with combination regimens including IMiDs and PIs showing promise[5,6]
- The corticosteroid dexamethasone (Dex) features prominently in combination regimens used to treat RRMM.[7] A combination regimen that is frequently recommended for both primary therapy and for the treatment of patients with RRMM includes Dex in combination with lenalidomide (Len)[8–10]
- The labeled dose of Dex in the Len–Dex combination is 40 mg given orally once daily on Days 1–4, 9–12 and 17–20 of each 28-day cycle, for a total of 480 mg[11]
- While the labeled dose of Dex (also known as high-dose Dex) has been shown to be effective in combination with Len in patients with RRMM, emerging evidence points to the increased use of low-dose Dex in Len–Dex regimens.[12–15] Low-dose Dex is given at a maximum dose of 160 mg/cycle, with 40 mg being given once daily on Days 1, 8, 15 and 22 of each 28-day cycle[15]
- An assessment of the frequency of use of high- versus low-dose Dex in patients with RRMM in real-world clinical practice in the United States will be informative

Objective

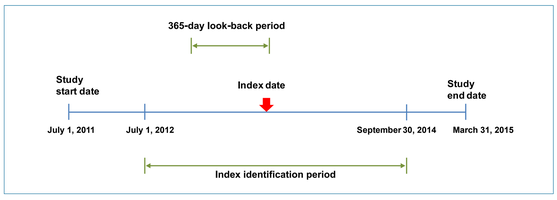
- To determine the average dose per cycle of Dex, when used in combination with Len, in patients with RRMM for the first 4 cycles as seen in real-world clinical practice in the United States
  - To determine this at the overall level across all lines of treatment (LOTs), by LOT, and by calendar year

Methods

Study design

- Analyses were conducted using claims data from the Truven Health Analytics MarketScan® Commercial and Medicare Supplemental databases (MarketScan® data)
- Patients with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for MM (203.0x) were identified via claims in the source databases between July 1, 2012 and September 30, 2014 (the index identification period) (**Figure 1**)
  - The index date for a patient was the earlier of the first MM diagnosis date and the first MM treatment date
  - The follow-up period was ascertained for each included patient based on the last enrollment date and prescription (Rx) eligibility

Figure 1. Schematic of the study design



Selection of patients

- Inclusion criteria
  - Diagnosis of MM during the index identification period, with at least one inpatient or ≥2 distinct outpatient diagnoses ≥30 days apart
  - At least one Rx claim for MM treatment during the index identification period
- Exclusion criterion
  - Age <20 years at index event

Cohorts of interest

- All the eligible patients were divided into 2 groups
  - Group 1: Newly diagnosed patients with MM who had continuous enrollment and Rx eligibility during the 365 days prior to the index date and who did not receive a Rx for MM treatment during this period
  - Group 2: Patients who had not been continuously enrolled during the 365 days prior to the index date, but who had continuous enrollment/Rx eligibility at the index date, and thus, for whom it could not be ascertained if they had received a prior Rx for MM treatment

Identification of RRMM LOTs

- For patients in Group 1, LOTs after the index date (and up to the end of the follow-up period) were identified using business rules described below. All Len–Dex lines after LOT1 were evaluated for this analysis, with the analysis also being carried out by LOT for this group of patients
- For patients in Group 2, LOTs after the index date (and up to the end of the follow-up period) were similarly identified. Since it is not certain that the first LOT is the front-line LOT in these patients, the first LOT was discarded and any Len–Dex LOTs among the remaining LOTs were evaluated since they were deemed to be relevant RRMM LOTs. The analysis was not stratified by LOT in these patients

Business rules for determination of LOTs

- The use periods of various relevant MM drugs were evaluated to isolate distinct periods of monotherapy or the combination regimen
- These distinct periods could be merged depending on the gap between them and whether the regimens were identical to, or represented a step-down or step-up from, each other

Determination of the dose per cycle of Dex

Evaluation of Dex dose per cycle

- The total strength (ie, the dispensed quantity multiplied by the unit strength) of all claims of Dex during the LOT evaluation period was aggregated for each patient, with the LOT evaluation period being defined as the period from the LOT start date to the earlier of the LOT start date plus 112 days or the LOT end date
- For any claim of Dex during the LOT evaluation period wherein the effective use period (based on the number of days' supply) exceeded the LOT evaluation period, only the dose relevant to the LOT evaluation period was apportioned and included in the analysis. Similarly, for any claim of Dex prior to the LOT evaluation period but wherein the effective use period encompassed part or all of the LOT evaluation period, the dose relevant to the LOT evaluation period was apportioned and included in the analysis

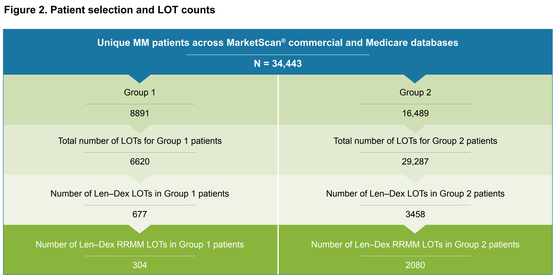
Evaluation measure

- Dose per cycle of Dex = A * 28 / B, where
  - A = total strength of Dex across all patients during the relevant period and in the relevant LOT
  - B = total LOT duration days that were evaluated for A

Results

- Of the 34,443 unique patients identified across the commercial and Medicare datasets in the MarketScan® database during the study period, 8891 and 16,489 patients were identified as belonging to Groups 1 and 2, respectively (**Figure 2**)
- The total number of distinct LOTs for patients in Groups 1 and 2 were 6620 and 29,287, respectively (**Figure 2**)
- The number of Len–Dex LOTs in the 2 groups were 677 and 3458, respectively, while Len–Dex RRMM LOTs accounted for 4.6% (n = 304) of all LOTs in Group 1 patients and 7.1% (n = 2080) of all LOTs in Group 2 patients (**Figure 2**)

Figure 2. Patient selection and LOT counts



Dex, dexamethasone; Len, lenalidomide; LOT, line of treatment; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma
Group 1: Patients with ≥365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date
Group 2: Patients with <365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date

- The median (interquartile range [Q1–Q3]) Dex dose per cycle across the first 4 cycles in RRMM LOTs was 121 (75–156) mg in Group 1 and 102 (70–154) mg in Group 2 (**Table 1**)

Table 1. Overall dose (mg) per cycle of Dex in patients with RRMM for the first 4 cycles based on MarketScan® data (2011–2015)

	Overall (2011–2015)
Group 1	
N (patient + LOT)	304
Mean (SD)	121 (66)
Median (IQR)	121 (75–156)
Range	3–546
Group 2	
N (patient + LOT)	2080
Mean (SD)	112 (74)
Median (IQR)	102 (70–154)
Range	3–1062

IQR, interquartile range; LOT, line of treatment; SD, standard deviation
Group 1: Patients with ≥365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date
Group 2: Patients with <365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date

- The median dose of Dex per cycle across the first 4 cycles showed decreases in both Groups 1 and 2 during each of the years in the study period (**Table 2**)
- In Group 1, the median Dex dose was consistent across LOTs 2, 3 and 4 (137, 113 and 114 mg/cycle, respectively) (**Table 3**). More than 2/3 of these LOTs showed a Dex dose of ≤160 mg/cycle

Table 2. Dose (mg) per cycle of Dex in patients with RRMM for the first 4 cycles, by year, based on MarketScan® data (2011–2015)

Year	2011	2012	2013	2014	2015
Group 1					
N (patient + LOT)	Since Group 1 patients had a ≥365-day clear look-back period, data for 2011 are not available for them	14	112	154	24
Mean (SD)		134 (30)	133 (64)	114 (67)	100 (66)
Median (IQR)		146 (116–156)	136 (80–162)	107 (71–156)	88 (64–140)
Range		70–162	36–405	3–456	32–361
Group 2					
N (patient + LOT)	209	684	616	502	69
Mean (SD)	111 (58)	117 (75)	113 (74)	106 (69)	98 (78)
Median (IQR)	113 (76–155)	112 (74–159)	103 (70–155)	93 (66–148)	79 (60–137)
Range	9–390	4–640	3–1062	4–853	14–474

IQR, interquartile range; LOT, line of treatment; SD, standard deviation
Group 1: Patients with ≥365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date
Group 2: Patients with <365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date

Table 3. Dose (mg) per cycle of Dex in patients with RRMM for the first 4 cycles, by LOT, based on MarketScan® data (2011–2015)

LOT	2	3	4	5	6
Group 1					
N (patient + LOT)	104	94	48	27	21
Mean (SD)	131 (76)	116 (60)	119 (55)	106 (54)	115 (67)
Median (IQR)	137 (77–160)	113 (75–153)	114 (78–157)	100 (65–146)	107 (77–149)
Range	4–546	3–405	16–286	45–302	60–361

IQR, interquartile range; LOT, line of treatment; SD, standard deviation
Group 1: Patients with ≥365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date

- Analysis of the dose per cycle of Dex across the first 4 cycles in Group 1 by year and by LOT revealed the median dose to consistently be <160 mg throughout (**Table 4**). The same held true when the dose per cycle of Dex across the first 4 cycles in Groups 1 and 2 was analyzed by cycle, with the median dose across all 4 cycles consistently being <160 mg (**Table 5**)

Table 4. Dose (mg) per cycle of Dex in patients with RRMM for the first 4 cycles, by year and by LOT, based on MarketScan® data (2011–2015)

Year	2011	2012	2013	2014	2015
LOT 2					
N (patient + LOT)	Since Group 1 patients had a ≥365-day clear look-back period, data for 2011 are not available for them	12	51	38	3
Mean (SD)		131 (31)	141 (64)	118 (98)	91 (45)
Median (IQR)		138 (104–157)	140 (84–167)	98 (61–155)	72 (58–160)
Range		70–162	44–386	4–546	58–160
LOT 3					
N (patient + LOT)	Since Group 1 patients had a ≥365-day clear look-back period, data for 2011 are not available for them	2	36	48	8
Mean (SD)		154 (1)	137 (68)	102 (51)	100 (38)
Median (IQR)		154 (153–156)	137 (92–161)	81 (66–148)	88 (79–139)
Range		153–156	36–405	3–192	32–148
LOT 4					
N (patient + LOT)	Since Group 1 patients had a ≥365-day clear look-back period, data for 2011 are not available for them	None of the patients initiated LOT3 in 2012	18	28	2
Mean (SD)			104 (44)	129 (61)	86 (11)
Median (IQR)			82 (77–156)	126 (85–160)	86 (75–97)
Range			60–186	16–286	75–97

IQR, interquartile range; LOT, line of treatment; SD, standard deviation
Group 1: Patients with ≥365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date

Table 5. Dose (mg) per cycle of Dex in patients with RRMM for the first 4 cycles, by cycle, based on MarketScan® data (2011–2015)

LOT	1	2	3	4
Group 1				
N (patient + LOT)	301	293	218	148
Mean (SD)	127 (74)	120 (78)	128 (71)	112 (65)
Median (IQR)	120 (80–160)	86 (57–160)	101 (60–160)	80 (50–149)
Range	3–800	0–617	3–389	2–347
Group 2				
N (patient + LOT)	2064	1967	1519	1109
Mean (SD)	123 (80)	110 (77)	112 (75)	101 (66)
Median (IQR)	112 (77–160)	80 (48–149)	81 (53–149)	80 (39–131)
Range	1–747	1–1143	1–1371	1–933

IQR, interquartile range; LOT, line of treatment; SD, standard deviation
Group 1: Patients with ≥365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date
Group 2: Patients with <365 days of clear look-back period (with continuous enrollment and Rx eligibility) prior to the index date

Study limitations

- Given that MarketScan® is a claims database, the use of Dex as revealed by the database is only based on pharmacy fills based on claims, and cannot be considered to accurately represent the actual use by patients
- LOTs have been determined from claims data based on certain business rules and may not accurately reflect LOTs as prescribed in actual clinical practice

Conclusions

- This real-world study of Len–Dex use among patients with RRMM shows that the majority receive low-dose Dex, and confirms the growing use of low-dose Dex in this combination regimen in all LOTs
- These findings, as supported by additional analyses, may inform revision of treatment guidelines for RRMM

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Disclosures

Ravi Potluri is an employee of SmartAnalyst Inc, which was contracted by Bristol-Myers Squibb to conduct this study. Teresa Zyczynski and Catherine Davis are employees of Bristol-Myers Squibb. Ravi Vij has been contracted as a consultant by Bristol-Myers Squibb for this study.

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