Title

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ORIGINAL RESEARCH

Healthcare Costs Incurred by Patients with Multiple Myeloma Following Triple Class Exposure (TCE) in the US

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ABSTRACT

Introduction: Multiple myeloma (MM) is a malignancy of plasma cells; most MM patients will eventually relapse or become refractory to treatment. Treating MM patients remains a challenge since patients eventually progress through several lines of therapy (LOTs), requiring the use of multiple MM drug classes. We examined healthcare resource utilization (HCRU) and the costs incurred by MM patients following triple class exposure (TCE; defined as exposure to a proteosome inhibitor, an immunomodulatory agent, and an anti-CD-38 antibody).

Methods: Adult MM patients were selected from the MarketScan® commercial and Medicare supplemental databases (January 2009–February 2021). From this cohort, patients who had TCE and ≥ 1 subsequent LOT that occurred after January 1, 2017 were included in the study population. The initiation date for the first post-TCE LOT was defined as the index date. All-cause and MM-related HCRU and the associated costs were examined post-index date.

Results: A total of 85 MM patients with TCE who initiated ≥ 1 subsequent LOT post-TCE and had ≥ 1 year of follow-up post-index date

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were included in the study population; mean age on index date was 58.8 years, and 60.0% were male. The time from first-observed MM diagnosis until index date averaged 47.5 months. During an average follow-up of 20.9 months post-index date, 64.7% of patients (N = 55) initiated a second LOT and 35.2% (N = 30) received at least 3 LOTs. During follow-up, mean total all-cause healthcare cost per patient was $722,992 (equivalent to $34,578 per patient per month [PPPM]). Approximately 90.7% ($655,524 per patient) of the total all-cause healthcare costs were MM related, 66.0% of which were MM drug/infusion costs.

Conclusion: In this real-world US study, MM patients with TCE incurred high healthcare costs, with the majority being MM related and primarily attributed to MM drug and infusion costs.

Keywords: Healthcare costs; Healthcare resource utilization; Multiple myeloma; Triple class exposure

Key Summary Points

Why carry out this study?

Multiple myeloma (MM) is a malignancy of plasma cells and accounts for approximately 10% of all hematological cancers and 1.8% of all newly diagnosed cancer cases in the United States.

Most patients with this cancer will eventually relapse or become refractory to treatment. Thus, treating patients with MM remains a challenge, as these patients eventually progress through several lines of therapy (LOTs).

To gain a better understanding of the potential value of new therapies for treating MM, we utilized a large US administrative healthcare claims database to examine healthcare resource utilization and the costs incurred by MM patients following triple class exposure (TCE; defined as exposure to a proteosome inhibitor, an immunomodulatory agent, and an anti-CD-38 antibody) during January 2017 through February 2021.

What was learned from the study?

During an average follow-up of 20.9 months, the mean total all-cause healthcare cost per patient was $722,992 (equivalent to $34,578 per patient per month [PPPM]), of which the majority was MM related and primarily attributed to MM drug and infusion costs.

These study findings underscore the significant need to develop and make widely available other novel targeted therapies for the treatment of MM patients to potentially improve patient outcomes and reduce the healthcare economic burden of this patient population.

INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells and accounts for approximately 10% of all hematological cancers and 1.8% of all newly diagnosed cancer cases in the United States [1, 2]. In 2021 in the US, it is estimated that 34,920 new cases of MM will be diagnosed, and 12,410 deaths will be attributed to the disease [1, 3]. The median age at diagnosis is 69 years, males (new cases: 8.8 per 100,000) are more commonly affected than females (new cases: 5.7 per 100,000), and non-Hispanic Blacks have twice the incidence of Whites and other races [1, 3].

Since the late 1970s, the 5- to 6-year survival rate of MM patients has more than doubled, from 25 to 55% [4, 5]. This improvement in

patient outcomes has in part been attributed to the introduction of several drug classes of MM therapies in the last few decades, including proteasome inhibitors (PIs; bortezomib, carfil-zomib, and ixazomib), immunomodulatory drugs (IMiD; lenalidomide, thalidomide, and pomalidomide), targeted monoclonal antibod-ies (daratumumab, elotuzumab, and isatux-imab), selective inhibitor of exportin-1 (selinexor), and the BCMA-targeting anti-body–drug conjugate belantamab mafodotin. Despite widespread utilization of these thera-pies for the treatment of MM, the disease remains incurable, and most patients will eventually relapse or become refractory to treatment [4, 6]. As a result, treating patients with MM remains a challenge, as these patients eventually progress through several lines of therapy (LOTs). Currently used MM treatments in LOTs comprise doublet and triplet regimens containing multiple drug classes, a principal recommendation for the treatment of MM patients in the National Cancer Comprehensive Network (NCCN) 2021 guidelines [7].

There are several novel targeted therapies currently in development for the treatment of relapsed/refractory multiple myeloma (RRMM), and the treatment landscape is expected to rapidly evolve in the near future [4]. To gain a better understanding of the potential value of new therapies for treating patients with RRMM, who have triple class exposure (TCE) and lim-ited treatment options, it is important to have a current assessment of the healthcare resource utilization (HCRU) and economic burden for these patients. Towards this aim, we utilized a large US administrative healthcare claims data-base to examine HCRU and the costs incurred by MM patients with commercial insurance coverage following TCE, defined as exposure to a PI, IMiD, and anti-CD-38 antibody, during January 2017 through February 2021.

METHODS

Study Design and Data Source

This study was a retrospective observational cohort study that utilized the IBM®

MarketScan® Commercial Claims and Encoun-ters (CCAE) and Medicare Supplemental (MDCR) databases. The CCAE database is a fully adjudicated, paid medical and pharmacy insur-ance administrative healthcare claims database of over 130 million unique persons, including active employees, early retirees, COBRA con-tinuers, and their dependents insured by employer-sponsored health plans. The MDCR database is an administrative healthcare claims database for Medicare-eligible active and retired employees and their Medicare-eligible depen-dents from employer-sponsored supplemental plans. Both databases capture utilization and costs of inpatient and outpatient medical ser-vices and pharmacy services as well as patient demographics and enrollment status. Used pri-marily for research and containing only de-identified patient dataset, the CCAE and MDCR databases are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Study Population

The patients included in this study were adults (≥ 18 years of age) diagnosed with MM between January 1, 2009 and February 28, 2021. MM was identified according to the International Clas-sification of Diseases (ICD) 9th/10th Revision Clinical Modification codes, ICD-9: 203.0 × and ICD-10: C90.0x. Patients were required to have received at least one NCCN guideline-recommended MM treatment [6] (Supplementary Table 1) on or after their first observed MM diagnosis date, and to be contin-uously enrolled in a medical/pharmacy benefit plan for at least 12 months prior to their first-observed MM diagnosis. Patients diagnosed with other types of malignancies prior to their first-observed MM diagnosis dates were exclu-ded from the study population.

From this overall MM patient cohort, we identified the subset of patients who had TCE, defined as exposure to a PI, an IMiD, and an anti-CD38 targeted antibody, during treatment following the first-observed MM diagnosis. To estimate costs post-TCE, we also required that these patients have at least one subsequent LOT

post-TCE. The initiation date of the first LOT post-TCE was defined as the index date for patients in the TCE cohort. Post-TCE LOTs were required to have occurred after January 1, 2017, in order to capture contemporary HCRU and cost estimates. Furthermore, using survival duration after TCE as a proxy measure for "fitness" in this MM population who have already cycled through multiple LOTs, patients were required to have survived at least 1 year after their index date. Patients were followed until the end of the study period, continuous enrollment, or death, whichever occurred first.

Definitions of Treatment Regimens and LOTs

Each regimen was defined by a start date, end date, and a distinct regimen made up of one or more drugs. A patient could have received multiple treatment regimens in sequence during the course of treatment. Every occurrence of a treatment change (including augmentation and switching) or initiation of a new regimen after discontinuation of a previous one constituted a LOT change.

A regimen was formed by one or several NCCN-recommended medications (Supplementary Table 1) for MM identified from both medical and pharmacy claims during the first 60 days following the regimen initiation. The index treatment date was the initiation date of the index regimen (i.e., the date of the first claim for an identified MM treatment). Each regimen ended on either the discontinuation date or the date of treatment change, whichever occurred first. The date of treatment change was the initiation date of the next LOT. Changes in any agent ('targeted' or chemotherapy) within 60 days of the first treatment was not considered a LOT change.

Gaps were calculated as the days elapsed between the last day of supply of a dispensing and its subsequent dispensing. The maximum allowed gap was 90 days in this study. If a stem cell transplant (SCT) occurred prior to the end of a gap, another 6-month allowed gap was added after the SCT.

A medication was considered discontinued if it was not refilled within the maximum allowed gap after the expiration of supply days of the last dispensing. If the medication was identified from a claim using a Healthcare Common Procedure Coding (HCPCS) code, the days of supply was imputed using the recommended treatment schedule.

An augmentation was defined as receiving a new medication of interest at least 60 days prior to discontinuing any of the medications included in the current regimen. The date of initiating the new medication was considered the augmentation date. A switch was defined as receiving a new medication of interest with at least one medication of the current regimen discontinued prior to or within 60 days after the initiation of the new medication. The initiation date of the new medication was the switch date. The addition of chemotherapy agents (e.g., cyclophosphamide, doxorubicin, melphalan) constituted a LOT change.

A regimen was discontinued when all medications included in the regimen were discontinued or a treatment change occurred (including augmentation and switching). If only a corticosteroid remained after discontinuation of other therapies in the regimen, that was considered a regimen discontinuation.

If a patient used a maintenance therapy (e.g., lenalidomide or bortezomib monotherapy) within 6 months after a SCT, regardless of whether lenalidomide or bortezomib was part of the initial regimen, this was not considered switching and did not trigger a LOT change. The discontinuation date for the regimen was extended to the discontinuation of the lenalidomide or bortezomib monotherapy.

Demographic and Clinical Characteristics

For each patient in the TCE study cohort, demographic and clinical characteristics, including age, sex, health plan type, insurance type (Commercial or Medicare), US region of residence, Quan Charlson Comorbidity Index (QCI) score, and year of index date, were evaluated on the patients' index dates or during the 12 months prior to index dates. Additionally,

the time from first-observed MM diagnosis until index date was determined.

HCRU and Associated Costs

During the 12-month period prior to the patients' index dates, all-cause and MM-related (i.e., claims including an ICD-9/10 code indicating a MM diagnosis) HCRU, including the number of hospitalizations and days of inpatient stays, number of emergency room (ER) visits, number of outpatient visits, and number of pharmacy fills (all-cause only), were examined for all patients in the TCE study cohort. During the same period, all-cause and MM-related healthcare costs were also measured. MM-related healthcare costs are reported with a breakdown for inpatient cost, ER cost, outpatient cost, drug costs, drug infusion cost, SCT cost, and other healthcare costs, all of which were reported as the average cost per patient.

For the primary analysis of this study, healthcare costs—all cause and MM related—were examined during the follow-up periods after a patient's index date (i.e., after the first post-TCE treatment initiation) and were reported as the average cost per patient and as per patient per month (PPPM); results were reported for the overall TCE cohort, as well as for patients < 65 years (Commercially insured) who made up the vast majority (89.4%) of the study sample. The average monthly total and MM-related healthcare costs per patient were also extrapolated in order to estimate the total costs incurred for an additional duration (in this case, up to 40 months after a patient's index date).

Statistical Analyses

All analyses conducted in this study were descriptive. Means and standard deviations were reported for continuous variables and numbers and percentages for categorical variables. All statistical analyses were carried out using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Table 1 Characteristics of patients who initiated ≥ 1 LOT post-TCE

	N = 85
Age in, years,[a] mean (SD)	58.8 (7.6)
Age group, N (%)	
18–44	3 (3.5)
45–54	18 (21.2)
55–64	55 (64.7)
65–74	5 (5.9)
≥ 75	4 (4.7)
Sex, N (%)	
Male	51 (60.0)
Female	34 (40.0)
Health plan type, N (%)	
Comprehensive	12 (14.1)
Health maintenance organization (HMO)	9 (10.6)
Preferred provider organization (PPO)	30 (35.3)
Other	34 (40.0)
Insurance type, N (%)	
Commercial	76 (89.4)
Medicare	9 (10.6)
US region of residence, N (%)	
South	39 (45.9)
Midwest	21 (24.7)
West	17 (20.0)
Northeast	8 (9.4)
QCI score, mean (SD)	3.5 (3.1)
Index date year, N (%)	
2017	24 (28.2)
2018	27 (31.8)
2019	29 (34.1)
2020	5 (5.9)

Table 1 continued

	N = 85
Time in months from first-observed MM diagnosis to index date, mean (SD)	47.5 (26.4)

QCI Quan–Charlson Comorbidity Index score, *SD* standard deviation, *TCE* triple class exposure

[a] On index date

RESULTS

Characteristics of the TCE Cohort

A total of 85 MM patients who initiated at least one subsequent LOT post-TCE and had at least 1 year of follow-up post-index date were included in the study population. Among this patient cohort, mean age as of the index date was 58.8 years, and 60.0% were male (Table 1). Approximately one-third (35.3%) of patients had preferred provider organization (PPO) health plans (Table 1). Mean QCI score was 3.5 (Table 1).

The time from a first-observed MM diagnosis until index date averaged 47.5 months; the duration of the first LOT post-TCE was approximately 10.4 months.

HCRU and Costs Prior to the Index Date

During the 12 months prior to the index date there were, on average, 1.7 all-cause hospitalizations, 0.6 ER visits, and 88.5 outpatient visits per patient (Table 2). The average length of hospitalization stay was 16.1 days (Table 2). Mean total all-cause healthcare costs per patient were $439,871 (Table 2).

During the same 12-month period, there were 1.4 hospitalizations, 0.2 ER visits, and 69.9 outpatient visits per patient that were MM-related (Table 2). The average length of MM-related hospitalizations was 15.4 days (Table 2). Mean total MM-related healthcare costs per patient were $414,323, which represented 94.2% of total all-cause healthcare costs; on

Table 2 HCRU and costs during the 12 months prior to the index date[a]

All-cause HCRU, mean (SD)	
Number of hospitalizations	1.7 (3.2)
Length of inpatient stays in days	16.1 (30.8)
Number of emergency room visits	0.6 (1.1)
Number of outpatient visits	88.5 (107.7)
Number of pharmacy fills	42.5 (19.6)
All-cause total healthcare costs, mean (SD) [b]	$439,871 ($272,509)
MM-related HCRU, mean (SD)	
Number of hospitalizations	1.4 (2.7)
Length of inpatient stays in days	15.4 (30.6)
Number of emergency room visits	0.2 (0.4)
Number of outpatient visits	69.9 (84.8)
MM-related healthcare costs, mean (SD) [b]	
Inpatient cost	$51,097 ($131,615)
Emergency room cost	$449 ($1,230)
Outpatient cost	$58,850 ($68,016)
MM drug cost	$263,600 ($170,639)
MM drug infusion cost	$11,705 ($12,004)
Stem cell transplant cost	$24,893 ($71,356)
Other costs	$3,730 ($2,460)
Total costs	$414,323 ($260,961)

HCRU healthcare resource utilization, *LOT* line of therapy, *MM* multiple myeloma, *SD* standard deviation, *TCE* triple class exposure

[a] Index date, defined as the initiation date of first LOT post-TCE

[b] Average cost for all patients in the sample; patients may not have incurred a cost in every category

Table 3 Total all-cause healthcare costs and MM-related healthcare costs incurred following the index date[a]

	All patients $N = 85$	Patients < 65 years of age (Commercially insured) $N = 76$
Follow-up duration in months, mean	20.9	21.1
All-cause total healthcare costs per patient, mean[b]	$722,992	$749,503
All-cause total healthcare costs PPPM, mean[b]	$34,578	$35,473
MM-related healthcare costs per patient, mean[b]		
Inpatient cost	$89,668	$97,260
Emergency room cost	$1,007	$918
Outpatient cost	$105,076	$113,548
MM drug cost	$415,475	$419,288
MM drug infusion cost	$17,405	$18,239
Stem cell transplant cost	$21,123	$23,055
Other costs	$5,770	$5,937
Total costs	$655,524	$678,245

[a] Index date, defined as the initiation date of first LOT post-TCE
[b] Average cost for all patients in the sample; patients may not have incurred a cost in every category
LOT line of therapy, *MM*: multiple myeloma, *PPPM* per patient per month, *TCE* triple class exposure

average, of the total MM-related healthcare costs per patient, inpatient hospitalizations accounted for 12.3%, outpatient visits 14.2%, and MM drug and infusion costs 66.4% (Table 2).

Table 4 Extrapolation of average monthly all-cause healthcare costs to estimate cumulative costs incurred following the index date[a]

Month post-TCE LOT initiation	All-cause total healthcare costs
1	$34,578
2	$69,156
3	$103,734
4	$138,312
5	$172,890
6	$207,468
7	$242,046
8	$276,624
9	$311,202
10	$345,780
11	$380,358
12	$414,936
13	$449,514
14	$484,092
15	$518,670
16	$553,248
17	$587,826
18	$622,404
19	$656,982
20	$691,560
21	$726,138
22	*$760,716*
23	*$795,294*
24	*$829,872*
25	*$864,450*
26	*$899,028*
27	*$933,606*
28	*$968,184*
29	*$1,002,762*
30	*$1,037,340*
31	*$1,071,918*

Table 4 continued

Month post-TCE LOT initiation	All-cause total healthcare costs
32	*$1,106,496*
33	*$1,141,074*
34	*$1,175,652*
35	*$1,210,230*
36	*$1,244,808*
37	*$1,279,386*
38	*$1,313,964*
39	*$1,348,542*
40	*$1,383,120*

LOT line of therapy, *TCE* triple class exposure

[a] Index date, defined as the initiation date of first LOT post-TCE

Italicized costs are projected based on the dataset of patients included in this study with an average follow-up of 20.9 months

HCRU and Costs After Index Date

The average duration of follow-up post-index date was 20.9 months; 64.7% ($N = 55$) of patients initiated a second LOT post-TCE and 35.2% ($N = 30$) received ≥ 3 LOTs. Over this follow-up period, the mean total all-cause healthcare costs per patient were $722,992 (equivalent to $34,578 PPPM). Among patients < 65 years of age, the mean total all-cause healthcare costs per patient were $749,503 (equivalent to $35,473 PPPM).

During patient follow-up, approximately 90.7% ($655,524 per patient) of the total all-cause healthcare costs were MM related, and most (66.0%) of these costs were attributed to MM drug and infusion costs (Table 3). Among patients < 65 years of age, mean total MM-related healthcare costs per patient were $678,245; 90.5% of the total all-cause healthcare costs per patient were MM related (Table 3).

The average patient follow-up duration in this study was approximately 21 months. This is related to restricting the index date for post-TCE treatments to 2017 onwards to capture contemporary HCRU and associated costs. Therefore, we also extrapolated the total all-cause healthcare costs for a period of up to 40 months after the index date. When extrapolating beyond the average follow-up period of patients in this study, the cumulative all-cause healthcare costs incurred per patient at 24 months post-index date was estimated at $829,872, and at 36 months was estimated at $1,244,808 (Table 4).

DISCUSSION

This real-world study of MM patients in the US with TCE provides a contemporary view of the healthcare costs incurred by this patient population as they progress through multiple LOTs. During the follow-up period of 20.9 months, the mean total all-cause healthcare cost per patient was $722,992 (equivalent to $34,578 PPPM), of which approximately 91% were MM related. Our study findings reflect more recent cost estimates (through February 2021) and are generally consistent with those reported in the study by Madduri et al. in which patients were also identified from the MarketScan CCAE and MDCR databases. In that study, 154 MM patients were selected who had TCE and initiated at least one subsequent LOT between December 1, 2015 and September 30, 2018 [8]. Total all-cause healthcare costs were estimated at $37,033 PPPM in the 6 months (median follow-up) after initiation of another LOT post-TCE; MM-related healthcare costs represented 96% of total all-cause healthcare costs [8]. Also, similar to our study findings, over one-half of the monthly MM-related healthcare costs were attributed to MM drug and infusion costs.

The findings of our study also show that following TCE, MM patients continue to receive additional LOTs due to disease progression and accumulate more healthcare costs during their treatment journey. The economic burden of treating MM patients is also impacted by increasing trends in the incidence of MM in the US [3] and patients becoming refractory to

currently used MM drugs [6]. Triplet regimens containing IMiDs, PIs, and/or anti-CD38 targeted antibodies have been shown in clinical trials to induce more sustained clinical responses and progression-free survival compared to other MM treatments [9] and are recommended as the standard of care [7]. Additionally, newer medications (i.e., pomalidomide, carfilzomib, elotuzumab, daratumumab, ixazomib, and the bortezomib–lenalidomide combination) for the treatment of RRMM have demonstrated improved effectiveness over older therapies in a real-world US study [10]. However, the clinical benefits are diminished as patients continue to progress through multiple LOTs with shorter intervals between sequential LOTs, highlighting the unmet need in this patient population [10].

As the treatment landscape evolves for MM patients, it will be important to put into context the substantial cumulative healthcare economic burden associated with currently used MM treatments to better understand the potential value of newer therapies with novel mechanisms of action. Additionally, it will be necessary to take into consideration that these patients will often relapse and become refractory to currently used MM treatments, especially the accumulated clinical burden of patient exposure to multiple MM drug classes and the progression to increasingly resistant disease, which is ultimately indicative of worse patient outcomes [6, 10, 11].

This study was a retrospective observational cohort study that utilized the MarketScan CCAE and MDCR databases, and the study findings should be interpreted from the perspective of certain limitations. First, the number of MM patients with TCE who received at least one subsequent LOT post-TCE was small in this study, and future follow-up studies are warranted. The population included in this analysis represented those patients with Commercial insurance and/or employer-sponsored Medicare coverage, and the study findings may not be generalizable to MM patients with other insurance types. In this study, approximately 11% of the overall study population were ≥ 65 years of age, and further study is needed utilizing other data sources that may have higher representations of MM patients in this age group.

Additionally, due to the disproportionate regional distribution across the US of patient administrative claims contained within the data sources used for this study, other studies in specific US regions, as well as in other countries, may be needed to more fully understand the healthcare costs of MM patients with TCE.

Administrative healthcare claims filed for reimbursement may have contained erroneous coding and misdiagnoses, but likely to only a small extent due to the adjudication of the MarketScan databases. As it was an observational study, only associations between exposure variables and outcomes could be established, not causal inferences. The prescriptions identified in the claims databases reflected those filled by patients, and may not have captured all that were actually prescribed. Lastly, the treatments assessed in this study were approved at different times, and the utilization of drug combinations continued to evolve.

CONCLUSIONS

In this real-world US study, we found that the overall healthcare costs incurred by MM patients with TCE were high, averaging $34,578 PPPM, of which the majority was MM related and primarily attributed to MM drug and infusion costs. These study findings underscore the significant need to develop and make widely available other novel targeted therapies for the treatment of MM patients to potentially improve patient outcomes and reduce the healthcare economic burden of this patient population.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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