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ORIGINAL RESEARCH

Healthcare Costs of Multiple Myeloma Patients with Four or More Prior Lines of Therapy, Including Triple-Class Exposure in the United States

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ABSTRACT

Introduction: The treatment of multiple myeloma (MM) remains a challenge as patients eventually progress through several lines of therapy (LOTs), requiring use of multiple MM drug classes. In this retrospective US claims-database study, we examined the healthcare costs of patients with MM who received ≥ 4 prior LOTs, including triple-class exposure (TCE).

Methods: Adult patients with MM were selected from the IBM MarketScan Commercial and Medicare claims databases (1 January 2012–30 June 2021). Eligible patients were required to have received at least four prior LOTs, and TCE (i.e., received a proteasome inhibitor, immunomodulatory drug, and anti–CD38-targeted monoclonal antibody) after the first-observed diagnosis of MM. The index date was defined as the initiation date of the first subsequent LOT after meeting the eligibility criteria for the study, and this date had to be after 1 January 2017 to capture contemporary cost estimates. The primary outcome measurements were all-cause and MM-related healthcare costs after the index date.

Results: The study population included 68 patients with MM (63% men), with a mean age of 59.8 years. Mean duration from first-observed MM diagnosis until index date averaged 46.7 months. During a mean follow-up of

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21.9 months, total all-cause healthcare costs averaged US$757,386 per patient (equivalent to US$34,610 per patient per month). MM-related healthcare costs (US$670,561 per patient) contributed on average 88.5% to the total all-cause healthcare costs; the majority (67.2%) of MM-related healthcare costs were attributed to drug and infusion costs (US$450,952 per patient).
Conclusions: In this retrospective US claims-database study, patients with MM with ≥ 4 prior LOTs, including TCE, continued to experience high healthcare costs that were mostly attributable to anti-myeloma drugs and their administration.

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

Key Summary Points

Why carry out this study?

Treatment of multiple myeloma (MM) remains a challenge as patients eventually progress through several lines of therapy (LOTs), requiring the use of multiple MM drug classes.

In a previous study, we examined the healthcare costs incurred by patients with MM after they had triple-class exposure (TCE) and had received at least one subsequent LOT.

In this follow-up analysis, we have specifically examined the healthcare costs of patients with MM who received ≥ 4 prior LOTs, including TCE, to provide an assessment of the potential value of newer treatment options for these patients.

What was learned from the study?

During a mean follow-up of 21.9 months, total all-cause healthcare costs averaged US$757,386 per patient (equivalent to US$34,610 per patient per month).

MM-related healthcare costs (US$670,561 per patient) contributed on average 88.5% to the total all-cause healthcare costs; the majority (67.2%) of MM-related healthcare costs were attributed to drug and infusion costs (US$450,952 per patient).

In this retrospective US claims-database study, patients with MM who received ≥ 4 prior LOTs, including TCE, continued to experience high healthcare costs with most of these costs attributable to anti-myeloma drugs and their administration.

These findings emphasize the need for novel therapies for heavily pre-treated MM patients to reduce the healthcare economic burden of this patient population and improving patient outcomes.

INTRODUCTION

An estimated 34,920 patients in the United States in 2021 were diagnosed with multiple myeloma (MM), a relatively rare cancer, but the second most common hematological cancer [1, 2]. When initially diagnosed with MM, approximately two-thirds of patients are aged > 65 years, with the median age at diagnosis of 70 years [3]. Currently, MM is an incurable disease, and its clinical course is characterized by a succession of progressively shorter remissions and relapses until patients become refractory to available treatments.

Over the past few decades, the 5-year survival rate of MM patients has more than doubled [4, 5]. Improved patient outcomes have in part been due to the introduction of new MM drug classes, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and targeted anti-CD38 monoclonal antibodies (mAbs) [5–7]. The standard of care for newly diagnosed patients with active symptomatic MM (NDMM) is a triplet regimen containing a PI and/or IMiD in combination with a corticosteroid or chemotherapy. The National Comprehensive

Cancer Network (NCCN) clinical practice guideline (v3.2021) recommends the triplet regimens of bortezomib, lenalidomide and dexamethasone, and bortezomib, cyclophosphamide, and dexamethasone as preferred primary therapies for stem cell transplant (SCT)-eligible patients and SCT-ineligible patients with NDMM [8].

Although these triplet regimens have been widely utilized in recent years among newly diagnosed patients, most patients eventually relapse or become refractory to treatment [9, 10]. Subsequent treatment regimens typically consist of doublet or triplet regimens that contain different combinations of one or more PIs, IMiDs, or mAbs with corticosteroids and/or chemotherapy. However, these successive lines of therapy (LOTs) have generally resulted in shorter durations of responses, decreased depth of responses, and lower survival rates [11, 12]. Once a patient has relapsed after having received regimens that contained a PI, IMiD, and anti-CD38 mAb, they are considered to be triple-class exposed (TCE). TCE patients have limited treatment options and worse clinical outcomes [13, 14]. In the Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure (MAMMOTH) study, median overall survival of TCE patients was 9.2 versus 11.2 months for patients who were refractory to only one other MM drug class; median overall survival further decreased to 5.6 months among TCE patients who were refractory to multiple PIs and IMiDs [14]. Previously, we assessed the healthcare costs incurred by patients with MM after they were TCE and had received at least one subsequent LOT [15]. In this follow-up study, we have specifically examined the healthcare costs of patients with MM who had received $\geq$ 4 prior LOTs, including TCE, to provide a better understanding of the potential value of new treatment options for these patients.

METHODS

Study Design and Data Source

This was a retrospective US claims-database study that used the IBM® MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental (MDCR) databases. These databases capture utilization and the associated costs of inpatient and outpatient medical services and pharmacy services, in addition to patient demographics and enrollment status. Only de-identified patient data are contained within the CCAE and MDCR databases and they are both fully compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Study Population

Adult patients ($\geq$ 18 years of age) diagnosed with MM between 1 January 2012 and 30 June 2021 were selected from the MarketScan CCAE and MDCR databases. MM was identified according to International Classification of Diseases (ICD), Ninth/Tenth Revision Clinical Modification codes (ICD-9: 203.0x; ICD-10: C90.0x). Patients were required to be continuously enrolled in medical/pharmacy benefit plans and not exposed to MM treatments for at least 12 months prior to their first-observed MM diagnosis. Patients diagnosed with other malignancies prior to the first-observed MM diagnosis date were excluded from the study.

At the index date, patients were required to have received at least four prior LOTs, including TCE, defined as having received a PI, IMiD, and anti-CD38 targeted mAb recommended by the NCCN guideline [8] after their first-observed MM diagnosis. The index date was defined as the initiation date of the first subsequent LOT after meeting the eligibility criteria for the study. Additionally, the index date was required to have occurred after 1 January 2017 in order to capture contemporary cost estimates. Lastly, patients were required to have had continuous enrollment in a medical/pharmacy benefit plan and to have survived at least 1 year after index date. Patients were followed until the end of the study period, continuous enrollment, or death, whichever occurred first.

Treatment Regimens and LOT Definitions

Treatment regimens and LOT definitions have been described in detail previously [15]. A summary of these methods is provided below.

Each treatment regimen was defined by a start and end date and was comprised of ≥ 1 MM medications recommended by the NCCN guidelines [8]. Medical and pharmacy claims were used to identify treatment regimens during the first 60 days after study initiation. The initiation date of the first (i.e., index) treatment regimen was the date of the first claim for an identified MM treatment, and that regimen ended on the discontinuation date or date of treatment change (i.e., augmentation or switching), whichever occurred first. Each treatment regimen change or start of a new regimen was considered to be a LOT change. Changes in any agent ('targeted' or chemotherapy) within 60 days of first treatment was not considered a LOT change.

A treatment gap was the number of days from the last day of supply to next date of dispensing, with a maximum allowable gap of 90 days. SCT before the end of a gap added a 6-month allowed gap. No medication refilled within the maximum allowed gap after supply days expired was considered to be a treatment discontinuation. Medications identified from the Healthcare Common Procedure Coding System (HCPCS) codes used the number of days supplied from the recommended treatment schedule.

Augmentations were when a patient started a new MM medication recommended by the NCCN guideline within 60 days prior to discontinuation of any of the treatments in the current regimen. A switch was when a new MM medication recommended by the NCCN guideline was started and at least one medication in the current regimen was discontinued within 60 days of beginning the new medication. Addition of chemotherapy agents (e.g., cyclophosphamide, doxorubicin, melphalan) was considered to be a LOT change.

A treatment regimen was discontinued once all medication in the regimen (corticosteroids not considered) were discontinued or an augmentation/switching occurred. Use of maintenance therapy (e.g., lenalidomide or bortezomib monotherapy) within 6 months after SCT was not considered to be switching or a LOT change. The regimen discontinuation date was extended until the discontinuation of maintenance therapy.

Demographic and Clinical Characteristics

For each MM patient included in the study population, 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 their index date or during the 12-month baseline period.

Healthcare Resource Utilization and Associated Costs

Over the 12-month period prior to index date, all-cause and MM-related (i.e., claims including an ICD-9/10 code indicating an MM diagnosis) healthcare resource utilization (HCRU) costs and associated costs were examined for each patient. HCRU included 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). Average MM-related healthcare costs were reported for inpatient cost, ER cost, outpatient cost, drug costs, drug infusion cost, SCT cost, and other healthcare costs.

The primary outcome measures of this study were all-cause and MM-related healthcare costs that occurred after a patient's index date. These costs were reported as the mean cost per patient (such as total all-cause healthcare cost) or mean cost per patient per month (PPPM). Results are provided for the overall study cohort, in addition to the subset of patients who were < 65 years of age (Commercially insured), who made up the majority (91.2%) of the sample. The average monthly total all-cause healthcare costs per patient were also extrapolated to estimate the total all-cause healthcare costs incurred for up to 36 months after a patient's index date.

Statistical Analyses

All statistical analyses were descriptive and conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

A total of 68 patients with MM were included in this study. The mean duration from first-observed MM diagnosis until the index date averaged 46.7 months (Table 1). Among this patient sample, the mean age on index date was 59.8 years and 60.3% were male (Table 1). Most patients had a preferred provider organization (PPO) health plan (39.7%) (Table 1). Mean QCI score was 5.2 (Table 1).

HCRU and Associated Costs Prior to Index Date

During the 12 months prior to the index date, the average number of all-cause hospitalizations, ER visits, and outpatient visits were 1.6, 0.6, and 58.6, respectively, per patient (Table 2). The mean length of stay for all-cause hospitalizations was 15.6 days per patient (Table 2). Total all-cause healthcare costs per patient were a mean of $468,514 (all costs reported here are in US dollars) (Table 2).

Further, during this 12-month period, the average number of MM-related hospitalizations, ER visits, and outpatient visits per patient were 1.4, 0.2, and 45.9, respectively (Table 2). The mean duration of stay for MM-related hospitalizations was 15.2 days per patient (Table 2). Mean total MM-related healthcare costs per patient were $432,366, accounting for 93.1% of total all-cause healthcare costs on average (Table 2). Of the total MM-related healthcare costs, hospitalizations accounted for 10.7%, outpatient visits for 12.6%, and MM drug and infusion costs for 69.8% (Table 2).

Healthcare Costs Incurred After the Index Date

The mean duration of follow-up after the index date was 21.9 months (Table 3). During this follow-up period, total all-cause healthcare costs averaged $757,386 per patient (equivalent to $34,610 PPPM; Table 3). Among patients who were aged < 65 years ($N = 62$), the total all-

Table 1 Characteristics of patients who received ≥ 4 prior LOTs, including TCE

Patient characteristics	Values ($N = 68$ patients)
Age in, years[a,b], mean (SD)	59.8 (7.5)
Age group, years, N (%)	
18–44	1 (1.5)
45–54	11 (16.2)
55–64	50 (73.5)
65–74	1 (1.5)
≥ 75	5 (7.4)
Sex, N (%)	
Male	41 (60.3)
Female	27 (39.7)
Health plan type, N (%)	
Comprehensive	7 (10.3)
Health maintenance organization (HMO)	5 (7.4)
Preferred provider organization (PPO)	27 (39.7)
Other	29 (42.6)
Insurance type, N (%)	
Commercial	62 (91.2)
Medicare	6 (8.8)
US region of residence, N (%)	
South	32 (47.1)
Midwest	19 (27.9)
West	10 (14.7)
Northeast	7 (10.3)
QCI score, mean (SD)	5.2 (3.3)
Index date year, N (%)	
2017	18 (26.5)
2018	17 (25.0)
2019	22 (32.4)
2020	11 (16.2)

Table 1 continued

Patient characteristics	Values (N = 68 patients)
Time in months from first MM diagnosis to index date [b]*, mean (SD)*	46.7 (24.4)

QCI Quan-Charlson comorbidity index score, *LOT* line of therapy, *SD* standard deviation
[a]On index date
[b]Index date was defined as the initiation date of first subsequent LOT after meeting eligibility requirements for the study (i.e. received 4 or more prior LOTs, including TCE)

cause healthcare costs averaged $793,640 per patient (equivalent to $35,760 PPPM; Table 3).

During patient follow-up, MM-related healthcare costs ($670,561 per patient) contributed on average 88.5% to the total all-cause healthcare costs (Table 3). The majority (67.2%) of the MM-related healthcare costs were attributed to MM drug and infusion costs ($450,952 per patient; Table 3). Similarly, among patients who were aged < 65 years, mean total MM-related healthcare costs per patient were $700,541, representing on average 88.3% of the total all-cause healthcare costs per patient (Table 3).

When the average monthly all-cause healthcare costs incurred per patient were extrapolated, the cumulative costs incurred at 24 and 36 months after the index date were estimated at $830,632 and $1,245,948, respectively (Table 4).

DISCUSSION

In this retrospective US claims-database study of patients with MM who received ≥ 4 prior LOTs, including TCE, total all-cause healthcare costs averaged $757,386 per patient during a mean follow-up of approximately 22 months (equivalent to $34,610 PPPM). Approximately 88.5% of these costs were MM-related, with the majority (67%) of these costs largely attributed

Table 2 Healthcare resource utilization and associated costs during the 12 months prior to index date

Healthcare resource utilization and associated costs	Values
All-cause HCRU, mean (SD)	
Number of hospitalizations	1.6 (3.2)
Length of inpatient stay, in days	15.6 (32.4)
Number of emergency room visits	0.6 (1.3)
Number of outpatient visits	58.6 (28.6)
Number of pharmacy fills	63.8 (32.1)
Total all-cause healthcare costs, mean (SD)[a]	$468,514 ($287,662)
MM-related HCRU, mean (SD)	
Number of hospitalizations	1.4 (2.7)
Length of hospitalization stay, in days	15.2 (32.1)
Number of emergency room visits	0.2 (0.4)
Number of outpatient visits	45.9 (26.0)
MM-related healthcare costs, mean (SD)[a]	
Inpatient cost	$45,893 ($111,345)
Emergency room cost	$262 ($820)
Outpatient cost	$54,467 ($67,004)
MM drug cost	$289,820 ($198,741)
MM drug infusion cost	$11,937 ($12,001)
Stem cell transplant cost	$26,162 ($79,558)
Other costs	$3,825 ($2,654)

Table 2 continued

Healthcare resource utilization and associated costs	Values
Total costs	$432,366 ($258,634)

Index date was defined as the initiation date of the first subsequent LOT after meeting the eligibility requirements for the study (i.e. had received ≥ 4 prior LOTs, including TCE)
HCRU Healthcare resource utilization, *MM* multiple myeloma
[a]Average cost for all patients in the sample; all patients may not have incurred cost in each category

to MM drug and infusion costs ($450,952 per patient). These study findings are similar to those published previously among a larger sample of patients with MM who had TCE ($N = 85$) where total all-cause healthcare costs averaged $34,578 PPPM over a 21-month follow-up, amounting to $722,992 per patient, of which approximately 91% were MM-related (MM drug/infusion costs: 66% of MM-related costs) [15].

These findings are also consistent with a publication (study period: December 2015-September 2018) by Madduri et al., which reported average total all-cause healthcare costs of $37,033 PPPM among 154 patients with MM who had TCE and had initiated at least one subsequent LOT; MM-related healthcare costs represented 96% of the total all-cause healthcare costs in this study [16]. The findings of Madduri et al. also indicate that MM drug and infusion costs contributed over one-half of the monthly MM-related healthcare costs [16]. The findings of the current study, along with other published studies [15, 16], show that patients with MM who had TCE and advance through multiple LOTs continue to incur high healthcare costs, primarily attributed to MM drug and infusion costs. The high monthly and total healthcare economic burden for this heavily pre-treated MM patient population

Table 3 Total all-cause and MM-related healthcare costs incurred after the index date

Total all-cause and MM-related healthcare costs	All patients ($N = 68$)	Patients aged < 65 years (commercially insured) ($N = 62$)
Follow-up duration in months, mean	21.9	22.2
Total all-cause healthcare costs per patient, mean[a]	$757,386	$793,640
Total all-cause healthcare costs PPPM, mean[a]	$34,610	$35,760
MM-related healthcare costs per patient, mean[a]		
Inpatient cost	$79,001	$85,415
Emergency room cost	$862	$926
Outpatient cost	$115,084	$125,214
MM drug cost	$434,526	$444,715
MM drug infusion cost	$16,426	$17,472
Stem cell transplant cost	$18,674	$20,481
Other costs	$5,988	$6,317
Total costs	$670,561	$700,541

The index date was defined as the initiation date of first subsequent LOT after meeting eligibility requirements for the study (i.e. received ≥ 4 prior LOTs, including TCE)
PPPM Per patient per month, TCE triple-class exposure
[a]Average cost for all patients in the sample; all patients may not have incurred cost in each category; all costs given in US$

underscores the possible value from newer treatment options for these patients.

In this study, we specifically required that MM patients had received at least four prior LOTs at the index date, including TCE. These patients have experienced a considerable burden of exposure to multiple MM drug classes and are vulnerable to treatment failure and

Table 4 Extrapolation of average monthly all-cause healthcare costs to estimate cumulative costs incurred after index date

Month post-index date	All-cause total healthcare costs
6	$207,658
12	$415,316
18	$622,974
24	$830,632
30	$1,038,290
36	$1,245,948

The index date was defined as the initiation date of first subsequent LOT after meeting eligibility requirements for the study (i.e. received ≥ 4 prior LOTs, including TCE)

worsening outcomes in subsequent LOTs. In the MAMMOTH study, median overall survival duration of patients with MM declined as the patients became refractory to more MM medications, with those penta-refractory (refractory to anti-CD38 targeted mAb, 2 PIs and 2 IMiDs) having a median overall survival of only 5.6 months [14]. Across the entire study cohort ($N = 275$; non-triple refractory: 21%; triple/quad-refractory: 54%; penta-refractory: 25%), median overall survival was only approximately 9 months [14]. Although more recently approved MM treatments, including pomalidomide, carfilzomib, elotuzumab, daratumumab, ixazomib, and bortezomib-lenalidomide combinations, have shown greater effectiveness in real-world populations of patients with MM, their clinical benefits were found to diminish as patients advanced through multiple LOTs [17], with these results indicating that these patients continue to experience a high treatment burden and are in need of novel therapies to improve outcomes.

This study was an observational, retrospective, US claims-database analysis that utilized the MarketScan CCAE and MDCR databases. Thus, the study findings should be interpreted in this context. First, the study population represents patients with US Commercial insurance and/or employer-sponsored Medicare coverage; as such, the study findings may not represent patients with MM who have varying insurance types or live in other countries. The MarketScan databases comprise claims with differing distributions across US regions. Furthermore, the databases consist of claims submitted by healthcare providers for reimbursement; as such, these claims may contain possible coding errors, i.e., coding for the purpose of rule-out rather than actual disease, and under-coding, without the possibility of verifying reported diagnoses. In this study, we defined MM-related HCRU as claims including an ICD-9/10 code indicating an MM diagnosis. This may have led to capturing some HCRU costs unrelated to MM; for example, patients with MM may have sought healthcare for other unrelated comorbidities and medical reasons and the providers may have included a diagnosis code indicating the patient had MM. However, this is a common method for identifying MM-related HCRU in health economics research studies [15, 17]. In the case of the measurement of pharmacy fills (all-cause only), the data only reflect those filled by patients and may not capture all that were actually prescribed. Additionally, the MM treatment regimens examined in this study were approved by the US Food and Drug Administration at different time periods, and MM drug regimens are continuing to evolve. Notably, the time frame of this study was mostly prior to the first approval of chimeric antigen receptor (CAR) T-cell therapy for the treatment of MM, and further study of this type of treatment on patients' healthcare costs is warranted.

CONCLUSIONS

In this retrospective US claims-database study, patients with MM who had received ≥ 4 prior LOTs, including TCE, continued to experience high healthcare costs, with most of these costs attributable to anti-myeloma drugs and their administration. Such findings emphasize that other novel therapies are still needed for improving outcomes and reducing healthcare economic burden in this heavily pre-treated MM patient population.

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Compliance with ethics guidelines. The data sources used in this study (i.e., the IBM® MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental (MDCR) databases) contain de-identified patient data sets and are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA).

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

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