Original Study

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Direct Medical Costs Associated With Treatment Nonpersistence in Patients With Higher-Risk Myelodysplastic Syndromes Receiving Hypomethylating Agents: A Large Retrospective Cohort Analysis

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Abstract

This study assessed medical costs of early discontinuation of hypomethylating agents (HMAs) in patients with refractory anemia with excess blasts subgroup of myelodysplastic syndromes using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (2010-2016). Patients discontinuing HMAs before the recommended time frame required to elicit clinical response may experience suboptimal outcomes and incur higher healthcare costs, thus pointing to the potential benefit of treatment continuity as per guidelines.

Background: Suboptimal use of hypomethylating agents (HMAs) among higher-risk myelodysplastic syndrome (HR-MDS) patients can translate into worse health outcomes and economic burden. We estimated the direct medical costs associated with HMA treatment nonpersistence among HR-MDS patients. **Patients and Methods:** Using the Surveillance, Epidemiology, and End Results—Medicare linked database, a retrospective cohort of patients diagnosed with refractory anemia with excess blasts (RAEB), a diagnosis that substantially overlaps with HR-MDS, between January 2011 and December 2015 was analyzed. Patients who had $\geq$ 1 year of continuous Medicare enrollment before diagnosis and who did not receive stem cell transplant or lenalidomide in the follow-up period were included. Patients receiving HMAs were stratified into HMA persistent ($\geq$4 HMA cycles) and HMA nonpersistent (<4 cycles or a gap of $\geq$ 90 days between cycles) groups. Healthcare resource use and costs during the follow-up period were reported descriptively as total and per patient per month (PPPM). Weighted generalized linear models (GLM) were used to compare estimated healthcare resource use and costs between HMA groups. **Results:** Among the 664 patients with RAEB, 295 (44.4%) were HMA nonpersistent and 369 (55.6%) HMA persistent. On the basis of weighted GLM analysis, the HMA nonpersistent group incurred significantly ($P < .05$) higher total PPPM costs compared to the HMA persistent group ($18,039 vs. $13,893), particularly for hospitalization ($3,375 vs. $2,131), and emergency room ($5,517 vs. $2,867) costs. **Conclusion:** There is a substantial economic burden associated with early discontinuation of guideline-recommended HMA therapy in RAEB patients. The study findings necessitate closer care management in this population in order to improve outcomes and reduce healthcare spending.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 21, No. 3, e248-54

Keywords: Healthcare resource use, Health economics, Persistence, Real-world studies, SEER database

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Submitted: Jul 28, 2020; Revised: Dec 2, 2020; Accepted: Dec 3, 2020; Epub: Dec 9, 2020

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https://doi.org/10.1016/j.clml.2020.12.002

Introduction

Hypomethylating agents (HMAs) are guideline recommended therapeutic options for patients with higher-risk myelodysplastic syndromes (HR-MDS).[1] HMAs have been associated with survival benefit, improvement in cytopenias resulting in delayed progression to acute myeloid leukemia,[2,3] and improved quality of life.[4]

HMA treatment is provided in multiple cycles, with each cycle comprising 5 to 7 consecutive days of azacitidine or decitabine administered intravenously or subcutaneously in the widely recommended schedules for patients with HR-MDS. However, there have been reported difficulties ensuring treatment cycles are administered as scheduled.[5] In their study among patients with MDS and other hematologic cancers, Tendas et al[6] reported a delay in 31% of the scheduled azacitidine cycles. Specifically the 7-day treatment schedule of HMA, which requires weekend administration, has been noted to be challenging for both patients and treatment centers.[7] In order to elicit clinical response, HMA treatment is recommended to be provided to patients for least 4, or even 6, treatment cycles.[8] Premature treatment discontinuation or suboptimal treatment is likely to affect clinical and economic outcomes. There is some evidence to suggest that underperformance (loss of response or inability to achieve a primary response) of HMAs is linked to premature termination of treatment cycles[9]; however, the economic impact of premature HMA treatment discontinuation is currently unknown.

The study objective was to estimate and compare the economic impact of HMA nonpersistence in patients with HR-MDS treated with HMAs.

Patients and Methods

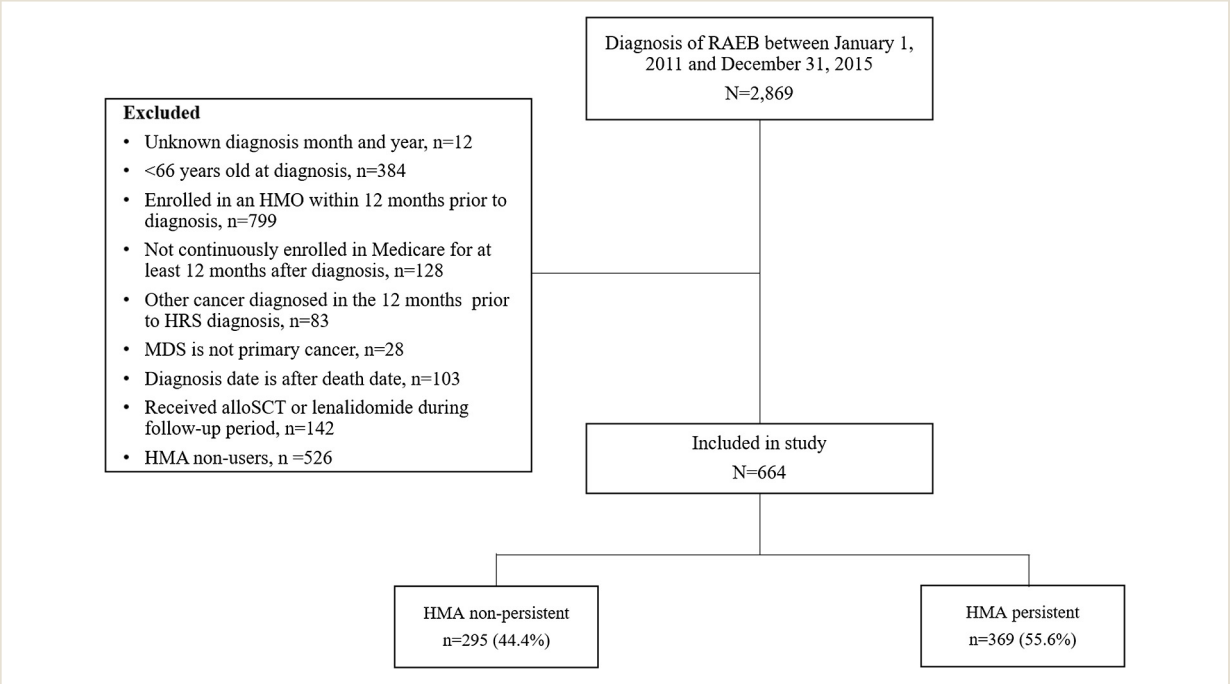
Study Design and Data Source

A retrospective observational cohort study utilizing the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database between 2010 and 2016 was conducted. The SEER dataset comprises regional cancer registry data, information on clinical and demographic characteristics, and cause of death for patients with cancer, linked to Medicare claims for covered healthcare services starting from the time of Medicare eligibility until death.[10]

Study Population

The study cohort included patients with an incident MDS diagnosis between January 1, 2011, and December 31, 2015. International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), code 9983/3 (refractory anemia with excess blasts [RAEB]) was used to identify HR-MDS, as RAEB is a histologic designation that often overlaps with International Prognostic Scoring System (IPSS) HR-MDS.[11,12] Patients were required to be $\geq$ 66 years of age at diagnosis and continuously enrolled in Medicare Parts A and B for $\geq$ 12 months before initial MDS diagnosis until the end of the study period, which was defined as censoring, death, or December 31, 2016, whichever occurred first. Patients with any other cancer diagnosis in the 12 months before their MDS diagnosis were excluded from this study. In addition, patients were excluded if at any point during the follow-up period they received an allogenic hematopoietic stem cell transplant or lenalidomide; had an MDS diagnosis date after their date of death;

Figure 1 Creation of Study Cohort



Abbreviations: alloSCT = allogeneic stem cell transplantation; HMA = hypomethylating agent; HMO = health maintenance organization; MDS = myelodysplastic syndrome; RAEB = refractory anemia with excess blasts.

Table 1 Baseline Demographic and Clinical Characteristics of Patients Stratified by HMA Persistence Status

Characteristic	All Patients (N = 664)	HMA Persistent (N = 369)	HMA Nonpersistent (N = 295)	*P*
Age at HR-MDS diagnosis (years), mean (SD)	77.81 (6.34)	77.3 (6.1)	78.4 (6.6)	.027
Male	413 (62.2)	239 (64.8)	174 (59.0)	.127
Race/ethnicity				.069
Non-Hispanic white	568 (85.5)	325 (88.1)	243 (82.4)	
Non-Hispanic black	32 (4.8)	17 (4.6)	15 (5.1)	
Hispanic/other	64 (9.6)	27 (7.3)	37 (12.5)	
Marital status at diagnosis[a]				.031
Unmarried	207 (31.2)	105 (28.5)	102 (33.6)	
Married	394 (59.3)	235 (63.7)	159 (53.9)	
Unknown	63 (9.5)	29 (7.9)	34 (11.5)	
Census location				.176
West	221 (33.3)	112 (30.4)	109 (36.9)	
South	182 (27.4)	110 (29.8)	72 (24.4)	
Northeast	151 (22.7)	89 (24.1)	62 (21.0)	
Midwest	110 (16.6)	58 (15.7)	52 (17.6)	
NCI Comorbidity Index[a]				.943
0-1	395 (59.5)	221 (59.9)	174 (59.0)	
2	78 (11.7)	42 (11.4)	36 (12.2)	
≥3	191 (28.8)	106 (28.7)	85 (28.8)	
Poor performance status	293 (44.1)	154 (41.7)	139 (47.1)	.165
Red blood cell transfusions within 8 weeks before first HMA[a]				.714
0	25 (3.8)	13 (3.5)	12 (4.1)	
≥1	639 (96.2)	356 (96.5)	283 (95.9)	
Platelet transfusions within 8 weeks before first HMA[a]				.729
0	184 (27.7)	98 (26.6)	86 (29.2)	
1	80 (12.0)	44 (11.9)	36 (12.2)	
≥2	400 (60.2)	227 (61.5)	173 (58.6)	
ESA before HMA[a]	78 (12.9)	40 (12.1)	38 (13.8)	.712
HMA type				.008
Azacitidine	518 (78.0)	302 (81.8)	216 (73.2)	
Decitabine	146 (22.0)	67 (18.2)	79 (26.8)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ESA = erythrocyte-stimulating agent; HMA = hypomethylating agent; HR-MDS = higher-risk myelodysplastic syndrome; MDS = myelodysplastic syndrome; NCI = National Cancer Institute.
[a]Total sample size and percentages are calculated for only those who received HMA.

or were enrolled in a health maintenance organization 12 months before and including the diagnosis month or if they had an unknown date of diagnosis (month or year). In addition, patients who did not initiate HMA treatment after MDS diagnosis were excluded from the study. The Advarra institutional review board granted this study exempt status because all patient data are deidentified.

Variables of Interest

Healthcare Common Procedural Coding System (HCPCS) codes J9025 (azacitidine) and J0894 (decitabine) were used to identify claims for HMA use in the data. Each HMA cycle was captured as claims for azacitidine/decitabine for 3 to 10 days during a 28-day period.[11-13] Demographic characteristics included age at the time of MDS diagnosis, sex (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/other), marital status at diagnosis (unmarried, married, unknown), and US Census region (West, South, Northeast, Midwest). Clinical characteristics included comorbidities ascertained using diagnosis codes in the baseline period (ie, 12 months before MDS diagnosis) using the National Cancer Institute Comorbidity Index (categorized as 0-1, 2, ≥ 3), a modified version of the Charlson comorbidity index.[6,14] Receipt of erythrocyte-stimulating agents before HMA initiation, blood transfusions (0, ≥ 1), and platelet transfusions (0, 1, ≥ 2) within the 8 weeks before HMA initiation were also identified. Finally,

poor performance status was included as a clinical covariate, identified as any claim for wheelchair use, oxygen use, walking aid, hospital bed, hospice care, or skilled nursing facility admission during the baseline period.

Outcomes

Patients were categorized on the basis of HMA treatment patterns as HMA persistent (≥4 cycles of either HMA) and HMA nonpersistent (<4 cycles or a gap of ≥ 90 days between cycles).

Healthcare resource use (HCRU) included physician visits, prescription drugs, outpatient visits, hospitalizations and associated length of stay, skilled nursing facility (SNF) visits, emergency room (ER) visits, durable medical equipment (DME), home health visits, and hospice visits. The HCRU and associated costs were calculated as per patient per month (PPPM). HCRU-related costs were reported as reimbursement amounts by Medicare by treatment setting including physician, prescription drugs, outpatient, inpatient, SNF, DME, home health agency, and hospice care. All costs were inflated to 2018 US dollars using the Consumer Price Index for medical care services and commodities.

Statistical Analysis

Patient demographics and clinical characteristics were summarized using descriptive statistics. Categorical outcomes were analyzed by Pearson chi-square tests or Fisher exact tests, and continuous outcomes were analyzed by ANOVA and Wilcoxon Mann-Whitney tests, as appropriate. To minimize the effect of selection bias, propensity score–based inverse probability of treatment weights (IPTW) were calculated to balance HMA-persistent and HMA-nonpersistent groups. First, the probability (propensity) of being in the HMA-persistent group was calculated using logistic regression that controlled for demographics, clinical characteristics, prior receipt of transfusions, type of HMA drugs, and poor performance status. Second, patient data were weighted by the inverse probability of the group assigned. To reduce the effect of extreme weights, stabilized weights were calculated. Stabilized weights were then used in the generalized linear models (GLMs), which compared the estimated HCRU and healthcare costs between HMA-persistent and HMA-nonpersistent groups. The GLM also controlled for baseline HCRU and costs. Cost analyses were conducted using log link and gamma distribution, while HCRU was assessed using negative binomial distribution. To study the effect of immortal time bias on our main findings, sensitivity analysis was conducted by restricting our analysis to patients who were alive for ≥ 4 months after MDS diagnosis. All analyses were conducted at an alpha level of .05 by SAS 9.4 software (SAS Institute, Cary, NC).

Results

A total of 664 patients diagnosed with HR-MDS (RAEB) who initiated treatment with HMA were included in the study (Figure 1). Of 664 patients, 369 (55.6%) were persistent and 295 (44.4%) were nonpersistent with HMA. The median follow-up for patients in the study was 12.3 months; longer follow-up was observed for HMA-persistent patients (13.3 months) compared to nonpersistent patients (9.5 months). Overall, patient characteristics between HMA-persistent and -nonpersistent groups were similar; however, compared to those with HMA persistence, those with nonpersistence were older at HR-MDS diagnosis, and a lower proportion of patients were married and initiated therapy with azacitidine (vs. decitabine) (Table 1). A more detailed comparison of characteristics can be found in Table 1.

Results from the IPTW-weighted regression analysis indicated that PPPM resource utilization was significantly higher among HMA-nonpersistent patients compared to HMA-persistent patients for hospitalizations, ER visits, and receipt of care via SNF, home health, and hospice. In contrast, the rate of outpatient and physician visits was significantly higher among HMA-persistent patients than HMA-nonpersistent patients (Table 2). These findings were also reflected in the weighted cost analyses. Compared to HMA-persistent patients, HMA-nonpersistent patients had significantly higher total costs as well as costs for hospitalization, ER, DME, and hospice care. Costs for prescription drugs, outpatient and physician services, and home health were similar between HMA-persistent and HMA-nonpersistent groups (Figure 2).

Sensitivity analysis among patients who were alive for ≥ 4 months suggested that HMA-nonpersistent patients had higher

Table 2 Weighted Healthcare Resource Utilization PPPM by HMA Persistence Status

Resource Type	HMA Persistent (N = 369) Mean (95% CI)	HMA Nonpersistent (N = 295) Mean (95% CI)	IRR (95% CI)	*P*
Hospitalizations	0.069 (0.058-0.082)	0.107 (0.087-0.132)	1.543 (1.181-2.018)	.001
ER visits	0.290 (0.265-0.317)	0.383 (0.342-0.428)	1.322 (1.146-1.524)	<.001
Length of hospital stay	1.796 (1.235-2.612)	4.090 (2.905-5.758)	2.277 (1.369-3.788)	.002
SNF visits	0.023 (0.016-0.032)	0.049 (0.033-0.072)	2.158 (1.308-3.560)	.003
DME use	0.263 (0.220-0.315)	0.342 (0.275-0.424)	1.299 (0.980-1.721)	.068
Hospice visits	0.065 (0.055-0.077)	0.165 (0.135-0.201)	2.555 (1.972-3.309)	<.001
Home health visits	0.057 (0.048-0.067)	0.076 (0.062-0.092)	1.335 (1.039-1.714)	.024
Outpatient visits	3.368 (3.114-3.643)	2.933 (2.671-3.220)	0.871 (0.771-0.984)	.026
Physician visits	13.760 (12.925-14.650)	16.925 (15.737-18.204)	1.230 (1.117-1.354)	<.001
Prescription drugs	2.981 (2.473-3.595)	2.896 (2.340-3.585)	0.972 (0.732-1.290)	.842

Abbreviations: CI = confidence interval; DME = durable medical equipment; ER = emergency room; HMA = hypomethylating agent; IRR = incidence rate ratio; PPPM = per patient per month; SNF = skilled nursing facility.

utilization rate for ER visits, hospitalizations, home health, hospice care, and SNF. Total healthcare costs were similar between HMA-persistent and -nonpersistent patients; outpatient costs were higher for HMA-persistent patients. However, costs for receipt of SNF, ER, and hospice remained significantly higher for the HMA-nonpersistent group compared to the HMA-persistent group (Tables 3 and 4).

Discussion

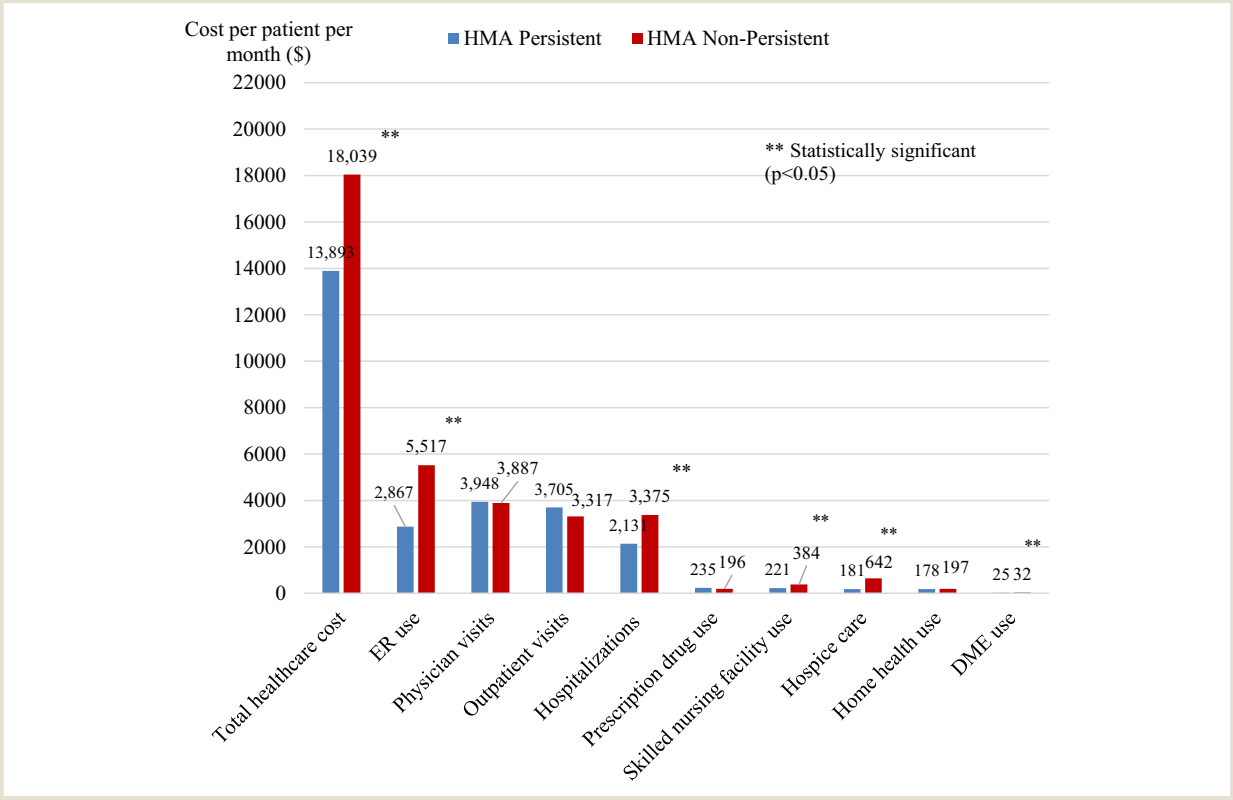
To our knowledge, this is one of the first large real-world studies using the SEER-Medicare data in HR-MDS patients reporting the association between HMA nonpersistence and resource use and associated costs. The study results point to a significant proportion of patients discontinuing HMA therapy before the clinically recommended duration to elicit a response to treatment. Further, we quantify the direct medical costs associated with premature discontinuation of HMAs or treatment nonpersistence, as indicated by higher resource use and costs in the HMA-nonpersistence group compared to the HMA-persistent group in patients who completed $\geq$ 4 cycles of therapy.

Our study showed that about half of the HR-MDS patients receiving HMA therapy did not persist with treatment; that is, they received < 4 cycles of HMA or had a gap ($\geq$90 days) in their treatment cycle. Although only a few studies have examined HMA treatment persistence,[15] Stein et al[16] evaluated HMA treatment success (defined as $\geq$ 7 HMA cycles, hematopoietic stem cell transplantation, or transfusion independence) or failure (defined as acute myeloid leukemia diagnosis, chemotherapy, or death) in patients with HR-MDS. They reported rates of HMA treatment success and failure as 44.4% and 76.2%, respectively, similar to those of HMA persistence and nonpersistence reported in our study.

This study also helps identify demographic and clinical characteristics related to HMA nonpersistence, which can help in the optimization of treatment for HR-MDS by taking these factors into consideration. There was a significantly higher proportion of older patients and those who were without a partner (unmarried or unknown marital status) in the HMA-nonpersistent group compared to the HMA-persistent group, suggesting that these patient subgroups may need more support getting to the treatment center to receive consecutive treatment cycles.

Our study findings complement those of previous retrospective claims database studies in quantifying direct medical cost in this population.[16] In terms of direct medical costs for HR-MDS patients, our findings reveal higher costs, particularly those with respect to hospitalization, ER, SNF, DME, and hospice among the nonpersistent patients, which reflects the downstream consequences of not continuing treatment cycles and premature HMA treatment termination. Cost estimates in our study were similar to those reported in other retrospective claims studies in this population. In

Figure 2 Weighted Healthcare Costs PPPM With HMA-Persistent and -Nonpersistent Treatment



Abbreviations: DME = durable medical equipment; ER = emergency room; HMA = hypomethylating agent; PPPM = per patient per month.

Table 3 Weighted Results for Healthcare Resource Use PPPM From Sensitivity Analysis After Restricting Patients Completing 4 or More Therapy Cycles

Variable	HMA Persistent (N = 362) Mean (95% CI)	HMA Nonpersistent (N = 214) Mean (95% CI)	IRR (95% CI)	*P*
Hospitalizations	0.069 (0.058-0.082)	0.088 (0.071-0.109)	1.271 (0.966-1.674)	.087
ER visits	0.280 (0.256-0.307)	0.325 (0.289-0.366)	1.160 (1.002-1.344)	.047
Length of hospital stay	1.794 (1.238-2.600)	3.063 (2.074-4.521)	1.707 (0.996-2.926)	.052
SNF visits	0.022 (0.016-0.031)	0.043 (0.028-0.064)	1.896 (1.125-3.194)	.016
DME use	0.249 (0.208-0.299)	0.291 (0.230-0.370)	1.169 (0.866-1.578)	.308
Hospice visits	0.063 (0.053-0.074)	0.112 (0.091-0.137)	1.775 (1.366-2.305)	<.001
Home health visits	0.055 (0.047-0.065)	0.074 (0.060-0.090)	1.340 (1.035-1.735)	.026
Outpatient visits	3.385 (3.128-3.663)	2.848 (2.566-3.161)	0.841 (0.738-0.959)	.01
Physician visits	13.486 (12.722-14.295)	13.358 (12.374-14.419)	0.991 (0.900-1.091)	.846
Prescription drugs	3.022 (2.495-3.659)	2.765 (2.154-3.549)	0.915 (0.668-1.253)	.58

Abbreviations: CI = confidence interval; DME = durable medical equipment; ER = emergency room; HMA = hypomethylating agent; IRR = incidence rate ratio; PPPM = per patient per month; SNF = skilled nursing facility.

another study, hospitalization cost was a significant driver of total healthcare costs among HR-MDS patients treated with HMAs.[16,17]

Our study has a number of strengths and limitations. The SEER-Medicare database is a database suitable for studying outcomes among the population aged 65 years and older. The database provides a wealth of cancer-related variables as part of the registry data, which complements data obtained via Medicare claims. Further, this database has been previously used to study outcomes in MDS population.[11-13,18]

One important limitation of this study is that the SEER-Medicare data do not capture reasons for HMA treatment discontinuation to classify it as appropriate or inappropriate. Aside from clinical progression or significant adverse events, other possible reasons for discontinuation of HMA therapy include worsening of performance status, oncologists considering patients to be unfit for continuing HMAs or logistical access challenges of traveling to the treatment center for repeat HMA administration, and patient wishes. In addition, we used the RAEB designation as a proxy for HR-MDS, as has been done in prior publications,[12,18] given that IPSS/revised IPSS (IPSS-R) risk groups or the components needed to calculate these risk scores (such as specific blood cell counts and cytogenetics) are not available in the database. While RAEB often overlaps with IPSS higher-risk categories, there are rare patients with RAEB who would be classified as having lower-risk MDS by the IPSS/IPSS-R, while some patients with profound cytopenia and/or high-risk cytogenetics who have HR-MDS by IPSS/IPSS-R might not have increased blasts. We limit the generalizability of our study findings to MDS patients aged 65 and older and not enrolled in health maintenance organization plans.

Conclusion

A significant proportion of RAEB patients receiving HMA treatment discontinue their treatment prematurely, which results in substantial economic impact compared to patients in the HMA-

Table 4 Weighted Results for Healthcare Costs PPPM From Sensitivity Analysis After Restricting Patients Completing 4 or More Therapy Cycles

Variable	HMA Persistent (N = 362) US$, Mean (95% CI)	HMA Nonpersistent (N = 214) US$, Mean (95% CI)	*P*
Total healthcare cost	13701.88 (12893.93-14560.46)	13698.25 (12653.75-14828.96)	.996
Hospitalizations	2173.759 (1701.445-2777.187)	2552.627 (1853.516-3515.430)	.439
ER visits	2728.017 (2360.945-3152.161)	3633.578 (3010.731-4385.276)	.018
SNF use	224.526 (175.069-287.954)	423.391 (306.274-585.291)	.002
DME use	24.010 (20.374-28.295)	28.502 (23.026-35.280)	.212
Hospice care	181.220 (148.401-221.297)	449.757 (346.948-583.032)	<.001
Home health use	171.506 (140.047-210.031)	226.435 (174.031-294.620)	.101
Physician visits	3855.251 (3516.900-4226.154)	2866.187 (2543.475-3229.844)	<.001
Outpatient visits	3705.257 (3348.394-4100.153)	3046.297 (2670.663-3474.765)	.021
Prescription drugs	239.961 (199.439-288.718)	239.497 (188.214-304.753)	.99
Home health use	171.506 (140.047-210.031)	226.435 (174.031-294.620)	.101

Abbreviations: CI = confidence interval; DME = durable medical equipment; ER = emergency room; HMA = hypomethylating agent; PPPM = per patient per month; SNF = skilled nursing facility.

persistent group. The high proportion of patients in the HMA-nonpersistent group warrants closer care management to achieve better outcomes and reduced healthcare spending.

Clinical Practice Points

- Hypomethylating agents (HMAs) are standard-of-care treatments for patients with higher-risk myelodysplastic syndromes (MDS), which are recommended to be treated with at least 4 therapy cycles to elicit a clinical response as per guidelines.
- Study findings indicate the existence of a significant proportion of patients with nonpersistent HMA treatment, ie, discontinuing therapy before 4 HMA cycles.
- This study further estimated and compared the economic impact of HMA nonpersistence in patients with higher-risk MDS treated with HMAs. The HMA-nonpersistent group incurred higher total monthly per-patient costs compared to the HMA-persistent group ($18,039 vs. $13,893).
- Hospitalization costs ($3,375 vs. $2,131) and emergency room costs ($5,517 vs. $2,867) were higher in the HMA-nonpersistent group compared to those who received 4 or more HMA cycles.
- There is a need for a closer care management via reminders and follow-up to ensure that there are no treatment delays and/or discontinuations due to reasons other than those deemed clinically necessary. These strategies will help ensure better outcomes and reduce avoidable healthcare spending.

Acknowledgments

This study was sponsored by Taiho Oncology, Princeton, NJ. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, Centers for Medicare and Medicaid Services; Information Management Services (IMS) Inc; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Disclosure

A.M.Z. received research funding (institutional) from Celgene/BMS, AbbVie, Astex, Pfizer, MedImmune/AstraZeneca, Boehringer-Ingelheim, Trovagene, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics. A.M.Z. participated in advisory boards, and/or had a consultancy with and received honoraria from Taiho, AbbVie, Otsuka, Pfizer, Celgene/BMS, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Seattle Genetics, BeyondSpring, Trovagene, Takeda, Ionis, Amgen, Janssen, Epizyme, Syndax, and Tyme. A.M.Z. served on committees for clinical trials for Novartis, AbbVie, BMS/Celgene, Geron, and Janssen. A.M.Z. received travel support for meetings from Pfizer, Novartis, and Trovagene. N.J., H.K., and S.C. are employees of Pharmerit International, received consulting fees from Taiho Oncology in conjunction with this study. T.W. and K.H. are employees of Taiho Oncology.

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