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Pattern of Hypomethylating Agents Use among Elderly Patients with Myelodysplastic Syndromes

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Abstract

Little is known about how hypomethylating agents (HMAs) have been adopted into the treatment of myelodysplastic syndromes (MDS). We conducted a population-based study to assess the use of HMAs among 4,416 MDS patients (age ≥ 66 years) who were diagnosed during 2001–2005 and followed up through the end of 2007. Multivariate logistic regression models were utilized to evaluate the role of various patient characteristics. 475 (10.8%) patients had received HMAs by 2007, with the proportion increasing over time. Patients who were white (odds ratio (OR)= 0.66, 95% confidence interval (CI): 0.46–0.95), male (OR= 1.47, 95% CI: 1.19–1.82), young ($P_{\text{trend}} < 0.01$), more recently diagnosed (OR= 1.90, 95% CI: 1.54–2.34), had fewer comorbidities ($P_{\text{trend}} < 0.01$), or had a history of other cancer (OR=1.28, 95% CI: 1.00–1.63) were more likely to receive HMAs. Compared with patients with refractory anemia, those diagnosed with refractory anemia with excess blasts or refractory cytopenia with multilineage dysplasia had a higher chance to be treated with HMAs (OR = 3.52 and 2.32, respectively). Relatively few MDS patients were treated with HMAs during the introduction period of these agents, and multiple patient characteristics such as sex, comorbidities, and MDS subtype influence the likelihood a patient receives HMAs.

Keywords

myelodysplastic syndromes; chemotherapy; new agents; hematology - medical

Introduction

Myelodysplastic syndromes (MDS, also known as myelodysplasia) comprise a heterogeneous group of diseases affecting the hematopoietic stem cell and predominantly myeloid lineages and occur primarily in older adults. Median overall survival in patients

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with MDS ranges from 0.4 to 5.7 years, depending on age, degree of cytopenias, and/or cytogenetic abnormalities,^{1–3}. Allogeneic hematopoietic stem cell transplantation with or without induction chemotherapy, an option mainly for younger patients in good health, is the only known curative therapy for MDS⁴. Prior to 2004, supportive care, low-dose chemotherapy, or, in rare cases, immunosuppressive agents, were the only available treatments for those who were not deemed eligible for induction chemotherapy and allogeneic stem cell transplantation⁵.

Two hypomethylating agents (HMAs), azacitidine and decitabine, were approved by the US Food and Drug Administration for the treatment of MDS in 2004 and 2006, respectively, and they represent a distinct treatment modality. HMAs are the only agents known to improve the natural history of MDS⁶, as they inhibit methylation and result in the re-expression of previously silenced genes that are relevant for cell growth, differentiation, and apoptotic process. Randomized trials have demonstrated that HMAs are associated with improved response rates coupled with decreased transfusion requirements^{7–10}, improved quality-of-life¹¹, and increased survival compared with either supportive care or conventional chemotherapy¹². Moreover, compared with conventional chemotherapy agents, HMAs are better tolerated.

Despite the dissemination of clinical evidence supporting their use, little is known about how HMAs have been adopted for patients with MDS. A thorough understanding of factors associated with adoption of new therapies for hematological malignancies can help to identify opportunities to improve quality of care for all patients, as well as to identify subgroups who are less likely to receive appropriate care. Prior studies of patterns of care for adults with cancer have identified differences in treatment based on race, treatment setting, and socioeconomic status^{13–21}. In the present study, we worked with a very large, population-based cohort of MDS patients to evaluate the pattern and predictors of the use of HMAs.

Methods

The linked SEER-Medicare database is the result of joint efforts by the National Cancer Institute and the Centers for Medicare and Medicaid Services (CMS). The database contains information on cancer diagnosis, demographic and socioeconomic patient characteristics, and Medicare claims, which together provide a valuable framework for population-based studies of older adults. The SEER program consists of population-based tumor registries in 17 geographic areas, covering approximately 26.2% of the US population. Among individuals who were included in SEER files and 65 years or older between 1995 and 1999, 93% were found in the Medicare enrollment file²². To date, various studies have suggested that SEER-Medicare data provide an effective and reliable way to ascertain various types of treatment, including chemotherapy^{22–24}.

Since 2001, MDS has been reported to the SEER program using histology types based on the International Classification of Diseases for Oncology (3rd Edition, ICD-O-3) codes²⁵. These include (1) 9980: refractory anemia (RA); (2) 9982: RA with ringed sideroblasts (RARS); (3) 9983: RA with excess blasts (RAEB, including RAEB under the French-American-British classification and both RAEB-1 and RAEB-2 under the World Health Organization recommendation); (4) 9985: refractory cytopenia with multilineage dysplasia (RCMD); (5) 9986: MDS associated with 5q deletion; (6) 9987: therapy-related MDS; and (7) 9989: MDS, not otherwise specified. Multiple published studies have identified MDS patients from SEER to assess risk and prognostic factors of MDS^{2,3,26–30}.

Study Population

We identified a total of 4,416 incident MDS patients (ICD-O-3: 9980, 9982 – 3, 9985, 9987 and 9989) who were diagnosed during 2001 – 2005 at the age of 66 years or older, were alive in September 2004 (i.e. 3 months after the initial FDA approval of azacitidine for the treatment of MDS), had known month of diagnosis, were not identified from death certificates or autopsy only, had continuous Medicare Parts A and B coverage, and were not enrolled in a health maintenance organization during the period of interest (September 2004 – December 2007). For MDS patients with deletion of chromosome 5q (ICD-O-3: 9986), lenalidomide is considered standard of care. As lenalidomide is administered orally and not captured by the current SEER-Medicare database, we did not include MDS patients with deletion of chromosome 5q in this analysis. Only patients diagnosed at 66 years or older were included to ensure a minimum of 12 months of Medicare claims prior to MDS diagnosis^{31–33}. Azacitidine was approved for all subtypes of MDS on May 19, 2004, and was assigned a specific procedure code by CMS immediately afterwards. To allow an adequate run-in time, the analysis on azacitidine included 4,416 MDS patients who were alive at least 3 months after its approval (i.e. in September 2004). Decitabine received FDA approval for all subtypes of MDS in June 2006, but it was not covered by Medicare until October 2006. A total of 2,174 MDS patients who were alive in January 2007 were included to study the use of decitabine. Patients were followed up through December 31, 2007, or death, whichever occurred first.

Treatment Characteristics

Physician claims, hospital outpatient claims, and inpatient claims were searched to assess the use of HMAs, erythropoiesis-stimulating agents (ESAs), blood transfusion, and chemotherapy. The relevant International Classification of Diseases–Ninth Revision–Clinical Modification (ICD-9-CM) diagnosis and procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and revenue center codes were used to identify the various treatments.

Study Variables

Other variables of interest included age at diagnosis (66–69, 70–74, 75–79, 80–84 and ≥ 85 years), sex, race/ethnicity (white vs. non-white), histological subtype (as indicated by ICD-O-3 codes), comorbidities, median household income at the census tract level, time of diagnosis (before vs. after May 2004), and use of other chemotherapeutic agents. To measure comorbidities, we searched inpatient, outpatient and carrier files for claims during the 12 months prior to diagnosis. The claims were then used to calculate the Elixhauser comorbidity score (with Quan adaptation)^{34,35}, which has been widely used as a summary measure for comorbid conditions. Neighborhood socioeconomic status was measured by median household income at the census tract level from the 2000 US Census, which was considered a reasonable reflection of the characteristics of neighborhoods in which patients resided at or shortly after diagnosis³⁶. Median household income was categorized into three levels (<39,120, 39,120–55,159, and $\geq 55,160$ dollars).

Statistical Analysis

Frequencies and percentages were used to describe various characteristics of the study population. Multivariate logistic regression models were utilized to assess the use of HMAs with respect to clinical and demographic characteristics. For age, comorbidities, and median household income, tests for trend were conducted by using variables in their original, continuous form. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC). All significance tests were two-sided with $\alpha = 0.05$.

Results

The study included 4,416 incident MDS patients diagnosed during 2001–2005. A majority of these patients were white (88.3%), male (54.6%) and had at least one comorbid condition (84.5%) (Table I). 475 (10.8%) had received HMAs by the end of 2007. Of these 475 patients, 450 received azacitidine and 84 received decitabine. Of those who received both HMAs ($n = 59$), 55 were treated with azacitidine first, followed by decitabine. The proportion of patients receiving HMAs increased over time, from 1.8% (56 out of 3,038 patients) in 2004 to 9.6% (288 out of 2,989 patients) in 2006 (Figure 1). Among patients diagnosed in May 2004 or later, the median lag time between the diagnosis and the initiation of HMA treatment was 249 and 223 days for any HMAs or azacitidine, respectively.

More male patients underwent treatment with HMAs, and the sex gap widened over time (Figure 2). In 2004, 2.4% of male patients and 1.2% of female patients received HMAs, whereas in 2006, 12.1% of male patients and 6.8% of female patients received HMAs. Patients with three or more comorbid conditions were less likely to receive HMAs than those with fewer comorbidities (Figure 3). As expected, the use of HMAs differed by MDS subtype (Figure 4). Patients diagnosed with RAEB were most likely to receive HMAs (11.4% in 2005 and 31.0% in 2006), followed by patients with RCMD (8.6% in 2005 and 14.1% in 2006), while the use of HMAs was rare among RA and RARS patients.

Aside from patients with more aggressive subtypes of MDS (RAEB and RCMD), multivariate logistic regression analyses revealed that patients were more likely to receive HMAs if they were white, male, younger, had fewer comorbidities, had a history of other cancer, or were more recently diagnosed (Table I). Compared with white patients, patients of other race/ethnicity were less likely to be treated with HMAs [odds ratio (OR) = 0.66, 95% confidence interval (CI): 0.46–0.95]. Male patients had a 47% higher likelihood than females of undergoing treatment with an HMA (OR = 1.47, 95% CI: 1.19–1.82). The use of HMAs was significantly less common among older patients and patients with more comorbid conditions (p for trend <0.01 for both). Patients with a history of other cancer were more likely to be treated with HMAs (OR=1.28, 95% CI: 1.00–1.63). Compared with patients diagnosed with RA, those diagnosed with RAEB or RCMD were more likely to receive HMAs (OR = 3.52 and 2.32, respectively). As expected, patients diagnosed after the FDA approval of azacitidine were more likely to receive HMAs than those diagnosed earlier (OR = 1.90, 95% CI: 1.54–2.34). Neither neighborhood socioeconomic status nor geographic region of residency appeared to have an impact on whether a patient received HMAs.

We also analyzed the data in regards to the use of non-hypomethylating chemotherapeutic agents used in MDS/AML. As expected, the frequency of use of those chemotherapy agents was lower than that of HMAs and remained stable throughout the study period from 2004 to 2006 (detailed data not shown).

In addition, we looked at blood transfusion status and the use of ESAs in our study population. Only 4 of 475 patients (0.8%) who were treated with HMAs had received neither blood transfusion nor ESAs; in contrast, the percentage was 32.5% ($n = 1279$) among patients who were never treated with HMAs. Moreover, 279 of 475 (52.4%) MDS patients who were treated with HMAs had received blood transfusion and/or ESAs before the administration of HMA.

Discussion

This study represents one of the first to explore the patterns of HMA use in the management of MDS. The large, population-based cohort consisting of newly diagnosed patients

represents a unique strength. During 2004–2007, only 11% of MDS patients received HMAs. Patients were more likely to receive HMAs if they were white, male, young, had fewer comorbidities, had a history of cancer, were diagnosed with the MDS subtypes of RAEB or RCMD, or were diagnosed after the approval of azacitidine. In addition, HMA users were more likely to have received blood transfusion or ESAs than non-HMA users.

Interestingly, the use of HMAs in the current study population was lower than what was reported by another US study based on six consecutive cross-sectional surveys of hematology and medical oncology specialists between June 2005 and January 2007³⁷. In the surveys, physicians were asked to report the treatment of the last 4–10 MDS patients they saw. The study found that 16% of recently diagnosed MDS patients and 11% – 15% of established patients received azacitidine, while 2% of recently diagnosed patients and 0% – 4% of established patients were treated with decitabine³⁷. The patients reported by the physicians, especially those established patients, were actively managed at the time of survey. However, a proportion of MDS patients may be in a watch-and-wait status. As reported by the surveys, among recently diagnosed MDS patients, 24% of patients with lower-risk disease and 5% of those with higher-risk disease were monitored without treatment³⁷.

The current study population included all eligible MDS patients in the SEER-Medicare dataset, regardless of their treatment status; thus, compared with actively managed patients, a lower percentage of HMA use was expected. Hatoum et al.³⁸ reported that only 4.6% of MDS patients received HMA therapy in the MarketScan® database. The MDS patients were identified by using ICD-9 code 238.7, a non-specific code for MDS and other lymphatic and hematopoietic disorders. Thus, misclassification of disease status may have contributed to the observed low percentage of HMA therapy. Although the percentage of HMA use increased overtime, the percentage is still low, as suggested by findings from a MDS registry³⁹. In that study, MDS treatment information was collected for 290 recently diagnosed MDS patients during June 2006 – June 2008, a more recent time-frame than the current study (i.e. up until June 2008 in the registry as opposed to December 2007 in the current study). However, only 9% of patients received azacitidine and 7% received decitabine. Overall, few existing studies have assessed the use of HMAs in MDS patients and show a low percentage of HMAs use among MDS patients. We believe the findings from the current analysis are unique due to the confirmation of MDS diagnosis through SEER reporting and the large, population-based cohort of newly diagnosed patients.

This study shows that multiple patient characteristics such as age, sex, race, and comorbidities influence the chance of being treated with HMAs. Among different MDS subtypes, RAEB and RCMD patients had a higher likelihood of receiving HMAs, which is consistent with the categorization of RAEB and RCMD patients as high-risk⁴⁰. This is supported by the National Comprehensive Cancer Network's (NCCN) 2009 recommendation of azacitidine as the preferred therapy for patients with high-risk MDS, with decitabine as an alternative (http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf). Based on these recommendations, the rate of HMAs use identified in this study is surprisingly low. It is unclear why administration of HMAs remained low in its target group. Additional studies will be needed, to assess use of HMAs in MDS with longer follow-up time after the approval of HMAs and probably publication of the NCCN guidelines in 2009.

While HMAs have proven beneficial in terms of overall survival¹² and quality of life¹¹, there are several drawbacks to their use. They do not have curative potential, their response rates are relatively low⁴⁰, and their administration requires frequent clinic visits and can temporarily cause or worsen cytopenias. Therefore, the debate on whether HMAs should be

regarded as standard of care for high-risk MDS patients is still ongoing. Although HMAs have been incorporated into the NCCN guidelines, how they should be used remains a clinical challenge. Further research is needed to determine which MDS patients would benefit the most from receiving these novel agents.

For patients with MDS in conjunction with other complicating factors such as advanced age, comorbid conditions, and poor performance status, the decision between pursuing more or less intensive therapy remains difficult, as there is little formal evidence currently available to guide such decision-making⁴¹. With the aging of the population and the increasing incidence of MDS, this study should raise awareness of impediments to treatment in MDS and lead to future studies allowing for risk-stratified treatment and a multidisciplinary approach to treatment of patients with comorbidities.

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Figure 1.
The Use of Hypomethylating Agents over Time

Figure 2.
The Use of Hypomethylating Agents over Time, by Sex

Figure 3.
The Use of Hypomethylating Agents over Time, by Elixhauser Comorbidity Score

Figure 4.

The Use of Hypomethylating Agents over Time, by Elixhauser Comorbidity Score
 RA:Refractory anemia, RARS: refractory anemia with ring sideroblasts, RCMD: refractory
 cytopenia with multilineage dysplasia, RAEB: refractory anemia with excess blasts

Table 1

Patient Characteristics and the Use of Hypomethylating Agents among 4,416 MDS Patients, SEER-Medicare, 2001–2005

	Total n	Hypomethylating agents		Unadjusted OR (95% CI) *	Adjusted OR (95% CI) *
		Ever n (%)	Never n (%)		
Race					
White	3900	437 (11.2)	3463 (88.8)	1.00	1.00
Non-white	516	38 (7.4)	478 (92.6)	0.63 (0.45–0.89)	0.66 (0.46–0.95)
Sex					
Female	2005	161 (8.0)	1844 (92.0)	1.00	1.00
Male	2411	314 (13.0)	2097 (87.0)	1.72 (1.40–2.09)	1.47 (1.19–1.82)
Age (years)					
66–69	419	49 (11.7)	370 (88.3)	1.00	1.00
70–74	807	116 (14.4)	691 (85.6)	1.27 (0.89–1.81)	1.29 (0.89–1.86)
75–79	1135	158 (13.9)	977 (86.1)	1.22 (0.87–1.72)	1.31 (0.91–1.87)
80–84	1133	108 (9.5)	1025 (90.5)	0.80 (0.56–1.14)	0.85 (0.59–1.23)
85+	922	44 (4.8)	878 (95.2)	0.38 (0.25–0.58)	0.38 (0.24–0.59)
P for trend				<0.01	<0.01
Region					
Northeast	1008	100 (9.9)	908 (90.1)	1.00	1.00
West	1820	175 (9.6)	1645 (90.4)	0.97 (0.75–1.25)	0.93 (0.71–1.23)
Midwest	816	100 (12.3)	716 (87.7)	1.27 (0.95–1.70)	1.28 (0.93–1.76)
South	772	100 (13.0)	672 (87.0)	1.35 (1.01–1.81)	1.42 (1.02–1.98)
Median household income at the census tract level (dollars)					
<39,120	1352	143 (10.6)	1209 (89.4)	1.00	1.00
39,120–55,159	1352	134 (9.9)	1218 (90.1)	0.93 (0.73–1.19)	0.88 (0.68–1.16)
55,160+	1351	161 (11.9)	1190 (88.1)	1.14 (0.90–1.45)	1.14 (0.87–1.49)
Unknown	361	37 (10.2)	324 (89.8)	0.97 (0.66–1.41)	0.86 (0.55–1.34)
P for trend				0.53	0.73
Elxhauser comorbidity score					
0	684	103 (15.1)	581 (84.9)	1.00	1.00
1–2	1713	220 (12.8)	1493 (87.2)	0.83 (0.65–1.07)	0.84 (0.65–1.10)

	Total n	Hypomethylating agents		Unadjusted OR (95% CI) *	Adjusted OR (95% CI) *
		Ever n (%)	Never n (%)		
>2	2019	152 (7.5)	1867 (92.5)	0.46 (0.35–0.60)	0.46 (0.34–0.61)
P for trend				<0.01	<0.01
History of other cancer					
No	3218	334 (10.4)	2884 (89.6)	1.00	1.00
Yes	1198	141 (11.8)	1057 (88.2)	1.15 (0.93–1.42)	1.28 (1.00–1.63)
Subtype (ICD-O-3)					
RA (9980)	815	55 (6.7)	760 (93.3)	1.00	1.00
RARS (9982)	603	42 (7.0)	561 (93.0)	1.03 (0.68–1.57)	0.96 (0.63–1.46)
RAEB (9983)	484	117 (24.2)	367 (75.8)	4.41 (3.12–6.21)	3.52 (2.47–5.02)
RCMD (9985)	222	35 (15.8)	187 (84.2)	2.59 (1.64–4.07)	2.32 (1.45–3.69)
MDS, NOS (9989)	2243	223 (9.9)	2020 (90.1)	1.53 (1.12–2.07)	1.51 (1.11–2.07)
Date of MDS diagnosis					
Before May 2004	2079	161 (7.7)	1918 (92.3)	1.00	1.00
May 2004 or later	2337	314 (13.4)	2023 (86.6)	1.85 (1.51–2.26)	1.90 (1.54–2.34)

SEER: Surveillance, Epidemiology, and End Results Program

RA: refractory anemia, RARS: Refractory anemia with ring sideroblasts, RCMD: refractory cytopenia with multi-lineage dysplasia, RAEB: refractory anemia with excess blasts, MDS NOS: nontherwise specified

* OR: odds ratio; CI: confidence interval. Adjusted odds ratios were derived from a multivariate logistic regression model that simultaneously included all variables listed in the table.