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Research paper

Early treatment initiation in lower-risk myelodysplastic syndromes produces an earlier and higher rate of transfusion independence

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ABSTRACT

Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis resulting in refractory cytopenias. Red blood cell (RBC) transfusions can improve anemia; however, prolonged transfusion dependence (TD) is associated with increased morbidity and mortality. Disease-modifying therapy (DMT) for MDS can reduce transfusion requirements, although the optimum timing of DMT initiation is unclear. This retrospective study analyzed linked SEER registry and Medicare claims (2006–2012) to estimate the impact of DMT-initiation (azacitidine, decitabine, or lenalidomide) timing (≤ 3 vs. > 3 months from start of TD) on the likelihood of achieving transfusion independence (TI) among 508 TD patients with MDS. Mean time to DMT was 28 days for early initiators (n = 351) and 187 days for late initiators (n = 157). Fewer early initiators used erythropoiesis-stimulating agents before achieving TI versus late initiators (61.5% vs. 73.9%; $P = 0.007$). In multivariate analyses, early DMT initiation predicted TI achievement (HR, 1.69; $P < 0.001$); patients who met minimum active therapy-exposure requirements were more likely to achieve TI (HR, 2.12; $P < 0.001$). Higher rates of TI were associated with reduced time between onset of TD and DMT initiation. Similarly, patients meeting the minimum treatment-exposure threshold had higher TI rates.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell disorders that are characterized by dysplastic blood cell production resulting in anemia, neutropenia, and thrombocytopenia, as well as increased risk of acute myeloid leukemia (AML). Diagnosis is based on peripheral blood and bone marrow biopsy, with detection of MDS by the presence of abnormal hematopoietic cell morphology, cytopenia(s), and < 20% blasts. MDS primarily affect older adults, with a typical age at diagnosis of ≥ 65 years [1–4]. Between 60,000 and 170,000 people in the USA have been estimated to have MDS [5].

Classification of MDS is evolving, but generally relies on standard light microscopy and cytogenetic criteria [6,7]. Prognostic scoring systems, such as the Revised International Prognostic Scoring System (IPSS-R), incorporate disease features such as blood counts, blast percentage, and cytogenetic abnormalities, and are used by clinicians to estimate the risk of MDS transformation to AML and the patient's survival time [8]. In general, patients with lower-risk MDS may be vigilantly monitored, sometimes for years, without intervention until significant worsening of cytopenias, need for transfusions, or recurrent infections indicate a need to treat. Conversely, patients with higher-risk MDS are usually treated immediately due to the risk of progression to AML and shortened survival time.

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CPT, Current Procedural Terminology; DMT, disease-modifying therapy; ESA, erythropoiesis-stimulating agent; FDA, Food and Drug Administration; HCPCS, Healthcare Common Procedure Coding System; HMA, hypomethylating agent; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; MDS-NOS, myelodysplastic syndromes, not otherwise specified; PPY, per patient-year; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB, t-refractory anemia with excess blasts in transformation; RARS, refractory anemia with ring sideroblasts; RBC, red blood cell; RCMD, refractory cytopenia with multilineage dysplasia; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results; TD, transfusion dependence/transfusion dependent; TI, transfusion independence/transfusion independent; t-MDS, therapy-related MDS

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Anemia, the most common cytopenia in MDS, often necessitates red blood cell (RBC) transfusions. While transfusions temporarily relieve symptoms, blood transfusions from volunteer donors carry the risks of infections (bacterial and viral), iron overload, and transfusion-related acute lung injury [5,9–11]. Transfusion dependence (TD) is also associated with increased mortality [12] and higher healthcare costs [13,14]. Reduction or elimination of the need for transfusions may therefore significantly benefit patients with MDS. In recognition of this important clinical outcome, reduction in transfusion frequency (e.g., achievement of transfusion independence [TI]) is often the primary outcome of interest when seeking U.S. Food and Drug Administration (FDA) approval for new therapeutic agents in MDS [15].

Currently, there are two classes of agents that potentially reduce transfusion need in MDS: immunomodulatory drugs such as lenalidomide, and hypomethylating agents (HMAs) such as azacitidine or decitabine. Lenalidomide is approved by the FDA for the treatment of IPSS-defined Low- or Intermediate-1-risk MDS with a deletion of chromosome 5q [del(5q)]. The HMAs azacitidine and decitabine are approved for the treatment of all subtypes of MDS [16]. Depending on the setting (e.g., risk category, time since diagnosis), these agents can improve cytopenias, reduce transfusion burden, lengthen time to disease progression, and extend survival [16]. National guidelines specify that immunomodulatory drugs and HMAs are indicated as treatments when MDS patients become TD. However, these induction agents can produce toxic side effects such as myelosuppression, and there are no recommendations for the timing of initiating treatment. Deciding when to start treatment in MDS patients can therefore be challenging. Unfortunately, data on the relative benefits of early or later initiation of treatment are lacking.

2. Materials and methods

2.1. Study design and data

This was a retrospective cohort study using 2006–2012 Surveillance, Epidemiology, and End Results (SEER) registry data linked to Medicare claims data. SEER is a coordinated system of population-based cancer registries located across the USA. The SEER program collects cancer incidence and survival data from 18 geographic regions, together representing more than one quarter of the US population [17]. The SEER–Medicare database includes all claims paid by Medicare for each covered beneficiary, which include claims for transfusions, stem cell transplantations and other procedures, inpatient admissions, and outpatient services.

2.2. Study population and time frame

Using SEER, we identified patients with MDS between 2007 and 2011 who became TD and were treated with azacitidine, decitabine, or lenalidomide (disease-modifying therapy [DMT]) (Fig. 1). Codes 9980–9989 of the International Classification of Diseases for Oncology, Third Edition (ICD-O-3; [18]) were used to identify a diagnosis of MDS. Based on a prior study [19], TD was defined as a period during which an MDS patient had at least 1 transfusion in each of 2 consecutive 8-week periods, with the transfusions separated by < 8 weeks. This definition was derived from Malcovati et al. and Duong et al., both of whom defined TD using a single 8-week period [19,20]. To increase the specificity of our definition, we required evidence of qualifying transfusions in 2 consecutive 8-week periods. Receipt of a transfusion was determined based on the presence of a relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure or diagnosis code, Healthcare Common Procedure Coding System (HCPCS) code, Current Procedural Terminology (CPT) code, or revenue center codes for blood components other than platelets in a Medicare claim (Appendix A in Supplementary material). The codes went beyond those specific to RBC transfusion as some codes are general (e.g., HCPCS P9051 is for whole blood or packed cells) and because there is evidence that, while codes for RBC transfusion have near perfect specificity, their sensitivity ranges from 21% to 83%, depending on the study [21]. The study index date was defined as the date of the first transfusion within the 16-week period used to define TD (Fig. 1). Patients were excluded if they received their first MDS diagnosis > 3 months after becoming TD; if they were not continuously enrolled in fee-for-service Medicare Part A, Part B, or Part D from 6 months prior to the index date to 6 months after the index date; if they were diagnosed with AML (ICD-9-CM code: 250.0x) or high-risk MDS (ICD-9-CM code: 238.73) within 30 days of the MDS diagnosis; if they were ≤ 59 years of age at the index date; or if they did not receive a DMT during the TD period.

The comparison groups comprised early or late initiators of DMT. Early initiators were those who started DMT within 3 months of the start of TD; all others were late initiators (starting DMT > 3 months from the start of TD). Patients were observed for a variable follow-up period: until reaching TI, until the end of enrollment, or until the study end.

2.3. Study measures

All measures were constructed using SEER–Medicare claims including ICD-9-CM, ICD-O-3, HCPCS, revenue center, and CPT codes. The primary study outcome was the cumulative incidence of TI, defined as a transfusion-free period of at least 56 days. Patients who did not achieve TI by the end of follow-up were considered censored. Other measures included patient demographics (age, gender, and geographic region), disease characteristics, treatment type and timing, and minimum treatment exposure, defined as ≥ 3 cycles for lenalidomide or ≥ 6 cycles for HMA treatments.

Disease characteristics evaluated included the presence or absence of the del(5q) syndrome (ICD-O-3 code: 9986), time from MDS diagnosis to TD, and MDS disease category, using ICD-O-3 codes to separate patients into 4 categories: Category 1 included patients with refractory anemia (RA; ICD-O-3 code: 9980) or MDS with del(5q) syndrome (ICD-

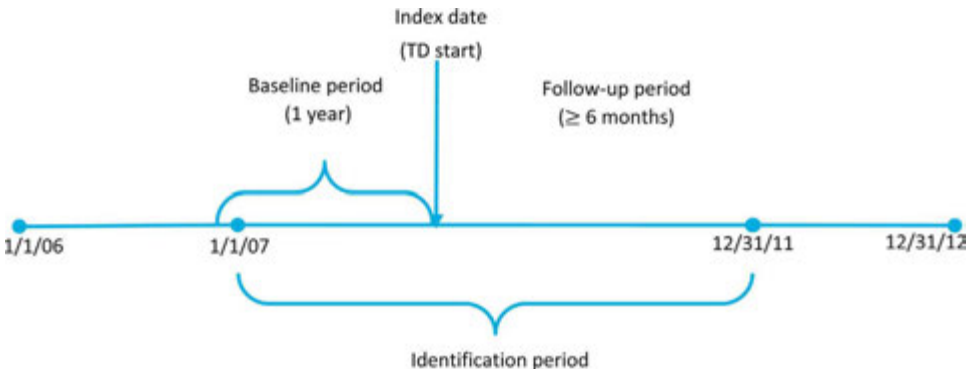

Fig. 1. Study time frame. Identification period: using SEER, we identified patients with MDS between 2007 and 2011 who became TD and were treated with azacitidine, decitabine, or lenalidomide (disease-modifying treatment). Index date: date of first transfusion within the 16-week period used to define TD. Dates are month/day/year.

O-3 code: 9986); Category 2 included patients with refractory anemia with ring sideroblasts (RARS; ICD-O-3 code: 9982); Category 3 included MDS, not otherwise specified (MDS-NOS; ICD-O-3 code: 9989); and Category 4 included refractory anemia with excess blasts (RAEB; ICD-O-3 code: 9983), RAEB in transformation (RAEB-t; ICD-O-3 code: 9984), refractory cytopenia with multilineage dysplasia (RCMD; ICD-O-3 code: 9985), and therapy-related MDS syndrome (t-MDS; ICD-O-3 code: 9987).

The primary exploratory variable of interest was early versus late treatment initiation, defined as the start of DMT within versus after 3 months from the study index date (start of TD). Other treatment-related variables included first DMT during TD, and use of erythropoiesis-stimulating agents (ESAs).

2.4. Statistical analysis

Descriptive statistics were generated for patient demographic, clinical, and treatment characteristics and reported for early versus late initiators and for all treated patients. Means and SDs were reported for continuous variables, and numbers and percentages for categorical variables. The primary outcome of TI was compared between early versus late initiators using unadjusted rates, Kaplan–Meier survival estimates, and multivariate Cox proportional hazards regression. For patients who did not reach TI, observation was censored at the end of follow-up (defined as end of enrollment, death, or study end). Cox models adjusted for a number of variables: age, gender, timing of MDS diagnosis relative to start of TD, MDS category (disease severity), ESA use during TD, and minimum treatment exposure. All data processing and analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

We identified 508 TD patients with MDS who had been treated with DMT. Of these patients, 351 met the definition of early treatment initiators, and the remaining 157 were classified as late treatment initiators. Considering all patients, the mean (SD) age at diagnosis was 76.2 (6.7) years. All US geographic regions were represented, and 45.5% of patients were female. Differences in demographic characteristics between study groups were not statistically significant (Table 1). The proportion of patients with del(5q) syndrome was similar for both groups (6.3% overall).

Disease severity varied between early and late initiators ($P < 0.001$), with more early initiators in Category 4, whereas > 70% of patients in each group had advanced Category 3 or 4 MDS. Timing of treatment also varied between groups. In the early initiator group, 92.3% had an MDS diagnosis before developing TD, compared with 71.3% in the late initiator group ($P < 0.001$). The remainder in each group had their first MDS diagnosis during the first 3 months after achieving TD (Table 1). The median follow-up period was 436 days for early initiators and 508 days for late initiators ($P = 0.032$).

By definition, early treatment initiators began treatment sooner compared with late initiators: the median time to starting DMT was 21 days in the early group versus 146 days in the late group. The proportion of patients receiving an HMA (azacitidine: 55.6% vs. 57.3%, decitabine: 24.8% vs. 18.5%) or lenalidomide (19.7% vs. 24.2%) was similar for early and late initiators ($P = 0.221$). Most patients received an ESA during their TD period, although ESA treatment was less frequent among early initiators compared to late initiators (61.5% vs. 73.9%; $P = 0.007$). Only a small proportion of early and late initiators met the minimum treatment exposure threshold for evaluating their respective DMT (37.4% vs. 36.9%; $P = 0.886$) (Table 2).

The median time to reach TI was significantly shorter in early compared with late initiators (284 days vs. 682 days; $P < 0.001$). The proportion of patients reaching TI was higher in early compared with late initiators at nearly all time points (Fig. 2). The unadjusted rate of achieving TI was also higher in early versus late initiators (0.72 per patient-year [PPY] vs. 0.40 PPY). This difference was observed irrespective of the minimum treatment exposure threshold being met (Table 3).

In adjusted analyses, early treatment initiation was associated with a significantly higher likelihood of reaching TI during the study period when compared with late initiation (HR, 1.69; 95% confidence interval [CI], 1.25–2.28; $P < 0.001$). Patients who met the minimum treatment exposure threshold were also significantly more likely to reach TI versus those who did not (HR, 2.12; 95% CI, 1.64–2.73; $P < 0.001$) (Table 4).

Table 1
Patient demographic and clinical characteristics.

	Early initiators (≤ 3 months) (n = 351)	Late initiators (> 3 months) (n = 157)	All treated patients (N = 508)	*P*
Age at diagnosis (SEER), years				
Mean (SD)	76.2 (6.8)	76.3 (6.4)	76.2 (6.7)	0.788
Median (range)	77 (38–89)	76 (60–91)	77 (38–91)	
Female, n (%)	151 (43.0)	80 (51.0)	231 (45.5)	0.097
Geographic region, n (%)				
Midwest	44 (12.5)	19 (12.1)	63 (12.4)	0.633
Northeast	70 (19.9)	39 (24.8)	109 (21.5)	
South	76 (21.7)	34 (21.7)	110 (21.7)	
West	161 (45.9)	65 (41.4)	226 (44.5)	
del(5q) syndrome, n (%)	21 (6.0)	11 (7.0)	32 (6.3)	0.661
MDS category, n (%)				< 0.001
1: RA or del(5q) syndrome	42 (12.0)	21 (13.4)	63 (12.4)	
2: RARS	15 (4.3)	19 (12.1)	34 (6.7)	
3: MDS-NOS	168 (47.9)	84 (53.5)	252 (49.6)	
4: Other MDS[a]	126 (35.9)	33 (21.0)	159 (31.3)	
Timing of MDS diagnosis relative to TD, n (%)				< 0.001
MDS diagnosis before TD	324 (92.3)	112 (71.3)	436 (85.8)	
MDS diagnosis ≤ 3 months after TD[b]	27 (7.7)	45 (28.7)	72 (14.2)	

MDS-myelodysplastic syndromes, MDS-NOS-myelodysplastic syndromes, not otherwise specified, RAEB-refractory anemia with excess blasts, RAEB-t-refractory anemia with excess blasts in transformation, RCMD-refractory cytopenia with multilineage dysplasia, RARS-refractory anemia with ring sideroblasts, SEER-Surveillance, Epidemiology, and End Results, TD-transfusion dependence/transfusion dependent, TI-transfusion independence/transfusion independent, t-MDS-therapy-related MDS.

[a] Other MDS includes: RAEB, RAEB-t, RCMD, or t-MDS.

[b] Patients who received an MDS diagnosis > 3 months after becoming TD were not included in the study.

Table 2
Treatment during transfusion dependence.

	Early initiators (≤ 3 months) (n = 351)	Late initiators (> 3 months) (n = 157)	All treated patients (N = 508)	*P*
Time from index to disease-modifying treatment, days				
Mean (SD)	28.0 (24.9)	187 (114.1)	77.2 (99.3)	
Median	21	146	42	
First disease-modifying treatment during TD, n (%)				
Azacitidine	195 (55.6)	90 (57.3)	285 (56.1)	0.221
Decitabine	87 (24.8)	29 (18.5)	116 (22.8)	
Lenalidomide	69 (19.7)	38 (24.2)	107 (21.1)	
Any ESA use during TD, n (%)	216 (61.5)	116 (73.9)	332 (65.4)	0.007
Met minimum treatment exposure threshold, n (%)[a]	132 (37.6)	58 (36.9)	190 (37.4)	0.886

ESA-erythropoiesis-stimulating agents, TD-transfusion dependence, TI-transfusion independence.

[a] Patients with ≥ 3 cycles of lenalidomide or ≥ 6 cycles of azacitidine or decitabine treatment without discontinuation during TD, or treated patients who reached TI before the minimum number of cycles.

4. Discussion

Our retrospective study using real-world SEER–Medicare data revealed that the early treatment of TD anemia among Medicare beneficiaries with MDS is associated with a higher rate and likelihood of achieving TI. The median time to TI among TD MDS patients who initiated DMT early was less than half the median time to TI for late initiators (Fig. 2). Early initiators also experienced a higher likelihood of reaching TI, with odds of attaining TI being 1.69 times that of late initiators (Table 4). Whereas a prior report showed that early introduction of ESA (within 8 weeks of becoming TD) was associated with a higher probability of achieving TI [19], this is the first report of the importance of disease-modifying treatment timing in MDS.

In this study, more patients in the early treatment group were diagnosed with MDS prior to becoming TD when compared with late initiators (92.3% vs. 71.3%; Table 1). This may indicate practice dynamics; physicians who are more likely to diagnose patients with MDS are also more likely to initiate DMT, and this may reflect differences in physician education, access to pharmacologic agents, or patient attitudes to receiving these therapies.

In addition, our analysis showed that extent of exposure to DMT had an independent effect on the likelihood of achieving TI. Specifically, the small proportion of MDS patients who received at least 3 prescription fills of lenalidomide or at least 6 cycles of an HMA had more than twice the likelihood of achieving TI compared with patients who had lower treatment exposure (Table 4). In general, this finding is consistent with previous studies of MDS patients, which showed increasing rates of TI with continued exposure to HMA or lenalidomide treatment (measured by number of administration cycles) [22–24]. However, these prior reports did not include adjusted comparisons of treatment exposure levels, in contrast to our study. Achieving TI is important, as extended dependence on transfusions is associated with increased morbidity [11], shorter survival [12,25], higher healthcare costs [5,26], and poor health-related quality of life [27–29]. These findings underscore the importance of keeping patients on therapy long enough for the patient to respond and achieve healthier outcomes.

Our study contributes to the literature in a few important ways. To our knowledge, this is the first study to examine how timing of DMT initiation affects the achievement of TI, and, in so doing, provides evidence of the clinical benefit of starting treatment soon after developing TD. Quite simply, patients who initiated DMT within 3 months were more likely to achieve TI and developed TD for a shorter period of time, decreasing transfusion-related risks such as infections, iron overload, transfusion-related organ injury, and mortality [5,9,10].

When considering the results of our study, a few limitations are noted. First, as with all observational studies, our analysis was subject to selection bias. We were not able to observe or fully adjust for all potential confounding factors that distinguished early and late initiators and that may be related to TI. However, our use of SEER registry data enabled accurate identification of MDS patients based on histology records, and we believe our analysis to be valid. Second, our study design used the start of TD, not treatment initiation, as the starting point (index date) for measuring time to TI; as a result, we can make inferences only about the impact of treatment initiation timing on TI, but not the impact of treatment itself. Additionally, the results on time to TI are also subject to lead-time bias, as time to TI for late initiators is a minimum of 3 months higher than that seen in the early initiator group. When we conducted a sensitivity analysis that controlled for timing of initiation, we found no difference in the time to TI between early and

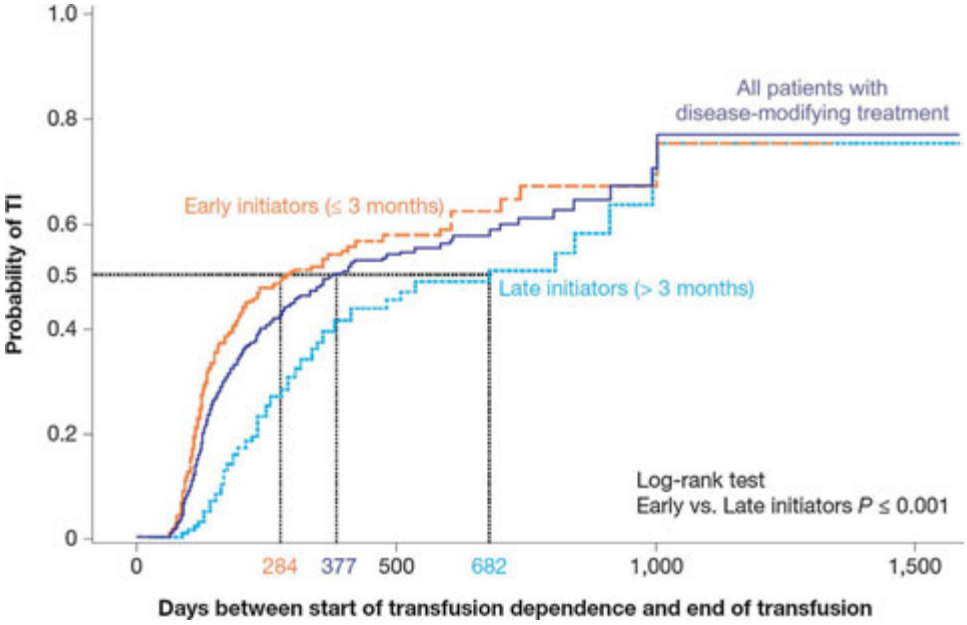

Fig. 2. Probability of patients reaching TI. Dotted lines indicate medians (number marked on horizontal axis in same color as corresponding plotted line for each group). TI-transfusion independence.

Table 3
Transfusion independence rate per patient-year.

	Early initiators (≤ 3 months) (n = 351)	Late initiators (> 3 months) (n = 157)	All treated patients (N = 508)
All patients on disease-modifying treatment, n	351	157	508
Patients who reached TI, n	189	67	256
Total TD patient-years[a]	262.5	167.6	430.0
TI rate PPY	0.720	0.400	0.595
Patients who met minimum treatment exposure threshold[b]	132	58	190
Patients who reached TI, n	95	38	133
Total TD patient-years[a]	93.7	62.4	156.1
TI rate PPY	1.014	0.609	0.852
Patients who did not meet minimum treatment exposure threshold[b]	219	99	318
Patients who reached TI, n	94	29	123
Total TD patient-years[a]	168.7	105.2	273.9
TI rate PPY	0.557	0.276	0.449

PPY-per patient-year, TD-transfusion dependence, TI-transfusion independence.
[a] For patients with TI, patient-years were the years from the index date to TI. For patients without TI, patient-years were the years from the index date to the end of follow-up.
[b] Patients with ≥ 3 cycles of lenalidomide or ≥ 6 cycles of azacitidine or decitabine treatment without discontinuation during TD, or treated patients who reached TI before the minimum number of cycles.

Table 4
Likelihood of reaching transfusion independence.

Variable	Adjusted[a] HR (95% CI)	*P*
Age, years		
60–69 vs. > 85	1.05 (0.67–1.65)	0.839
70–74 vs. > 85	0.67 (0.43–1.04)	0.072
75–79 vs. > 85	0.70 (0.46–1.07)	0.103
80–84 vs. > 85	0.58 (0.38–0.89)	0.013
Female vs. male	0.99 (0.77–1.28)	0.963
TD prior to MDS diagnosis, yes vs. no	0.84 (0.55–1.29)	0.430
MDS category[b]		
Category 2 vs. 1	0.37 (0.20–0.69)	0.002
Category 3 vs. 1	0.75 (0.52–1.09)	0.128
Category 4 vs. 1	0.67 (0.44–1.00)	0.052
Use of ESA during TD, yes vs. no	0.74 (0.57–0.96)	0.023
Met minimum treatment exposure threshold[c], yes vs. no	2.12 (1.64–2.73)	< 0.001
Early (≤ 3 months) vs. late (> 3 months) initiators	1.69 (1.25–2.28)	< 0.001

ESA-erythropoiesis-stimulating agent, MDS-myelodysplastic syndromes, MDS-NOS-myelodysplastic syndromes, not otherwise specified, RA-refractory anemia, RARS-refractory anemia with ring sideroblasts, TD-transfusion dependence.
[a] Adjusted for: patient demographics, timing of MDS diagnosis relative to start of TD, MDS category (disease severity), ESA use during TD, and minimum treatment exposure.
[b] Category definitions: 1, RA or del(5q) syndrome; 2, RARS; 3, MDS-NOS; 4, Other MDS.
[c] ≥ 3 cycles of lenalidomide or ≥ 6 cycles of azacitidine or decitabine without discontinuation during TD, or reached TI before the minimum number of cycles.

late initiators, indicating that time between treatment and TI is not influenced by timing of the treatment initiation per se. Third, Medicare claims data are not maintained for research purposes; therefore, to the extent that transfusion administrations are miscoded in claims, our measures of the number of transfusions, occurrence of TD, and occurrence of TI may be inaccurate. Finally, we studied timing of treatment initiation among Medicare beneficiaries; therefore, our findings may not be generalizable to other, younger, MDS patient populations.

5. Conclusions

Medicare beneficiaries with MDS who began DMT within 3 months of becoming TD were more likely to achieve TI than patients who initiated therapy after 3 months. Decreased transfusion burden confers important clinical benefits by reducing transfusion-associated morbidity. Patients who receive chronic blood transfusions are at risk of iron overload and related complications including diabetes, liver disease, organ damage, and cardiomyopathy; these patients also have a reduced overall survival [9]. Furthermore, patients with TD MDS have also been shown to be at risk of infection, reduced survival, and increased risk of death or progression to AML [9,11]. In terms of economic impact, a retrospective review of Medicare claims data found that even when differences in baseline clinical characteristics were taken into account, patients who received transfusions had higher healthcare costs and used more hospital services (both in- and outpatient) compared with those who did not receive transfusions [11]. Decreased transfusion burden may therefore lead to a significant benefit among patients with MDS. Follow-up research is needed on the potential cost savings of early treatment initiation. Studies of MDS clonal evolution may help to elucidate how early versus late treatment exposure impacts the subclonal architecture of MDS.

Disclosures

C.R.C. is a consultant for Partnership for Health Analytic Research, LLC, and is a Scientific Advisory Board member for the Celgene MDS/AML Connect Study. S.R.R., E.C., and M.S.B. are employed by Partnership for Health Analytic Research, LLC. E.P. was formerly employed by Partnership for Health Analytic Research, LLC. M.McG. is employed by and has equity ownership in Celgene Corporation. G.B. was formerly employed by and has equity ownership in Celgene Corporation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2017.07.008.

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