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Variations in erythropoiesis-stimulating agent administration in transfusion-dependent myelodysplastic syndromes impact response

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ABSTRACT

Introduction: Erythropoiesis-stimulating agents (ESAs) reduce red blood cell (RBC) transfusions in approximately 40% of patients with myelodysplastic syndrome (MDS) in clinical trials. We studied the association of timing of ESA initiation, agent (epoetin alfa, darbepoetin) and number of weeks of ESA use with response in MDS patients in routine practice.
Methods: Patients diagnosed with MDS from 2001 to 2005 were identified in the Surveillance Epidemiology and End Results-Medicare linked database. The study cohort consisted of patients with new-onset transfusion dependence (TD). All patients received an ESA at least once during the study period, which began the week that criteria for TD were met and continued until transfusion independence (TI). Kaplan–Meier statistics and Cox Proportional Hazard models were used to assess relationships between time to ESA initiation, agent and number of weeks of ESA use and TI attainment.
Results: Of 610 TD patients treated with ESAs, 210 (34.4%) achieved TI. Median time from ESA initiation to TI was 13 weeks. Shorter time from TD to ESA initiation and use of darbepoetin were associated with higher probability of achieving TI. The probability of achieving TI decreased beyond 8 weeks of treatment, and was very low beyond 16 weeks (8–15 weeks: HR = 0.64, 16–31 weeks: HR = 0.25, 32+ weeks HR = 0.10).
Conclusions: In this observational, population-based study, variations in ESA administration impacted response in transfusion-dependent MDS patients, with higher response rates with early administration and use of darbepoetin, and low response likelihood in non-responders beyond 16 weeks of therapy.

1. Introduction

Anemia is present in at least 85% of patients with myelodysplastic syndromes (MDS) at diagnosis [1], and significantly impacts quality of life. Erythropoiesis-stimulating agents (ESAs) ameliorate anemia associated with MDS in approximately 20% of unselected patients and 40% of lower-risk patients [2,3]. Response rates may be improved by selecting patients with low endogenous serum erythropoietin levels and low transfusion burden and by co-administering granulocyte colony-stimulating factor (G-CSF) [4–6].

While ESAs are commonly administered to MDS patients [7,8] and a randomized phase III trial provided evidence of efficacy compared to best supportive care in lower-risk disease [9], MDS remains an unapproved indication for these agents. Most published trials of ESAs in MDS have used significantly higher doses of epoetin alfa than those used for other indications, in the range of 40,000–80,000 U/week [10,11]. Thus response rates in routine practice may be lower than those reported in clinical trials if labeled dosing instructions for other indications are followed. The timing of ESA initiation may also affect response rates, as a shorter time interval between diagnosis and treatment with ESAs has been correlated with increased response rates [12]. Finally, the value of continuing ESAs in the absence of an early response is unclear. Treatment guidelines recommend modifying therapy in patients who have not manifested an increase in hemoglobin level or a decrease in red

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blood cell (RBC) transfusion requirements after ESA administration for 6–8 weeks [13,14].

We used cancer registry data linked to Medicare claims to study the impact of variations in ESA administration on treatment response. Because the Surveillance Epidemiology and End Results (SEER)-Medicare database does not include data on blood counts, we limited the study population to patients receiving RBC transfusions and measured the impact of ESA therapy on cessation of transfusions.

2. Methods

2.1. Study population

MDS cases newly reported between 2001 and 2005 were identified from SEER data matched to Medicare enrollment and claims files [15]. Patients were required to have ≥1 claim for an ESA while transfusion-dependent (TD), as defined below. Patients were excluded if they had a history of chronic renal failure, if the diagnosis or death dates were not recorded, if they were not continuously enrolled in Medicare Parts A and B, or were enrolled in Medicare Advantage during the 12 months prior to, or any time after, diagnosis.

2.2. Study endpoints

A weekly measure of transfusion status was created based on the frequency and timing of claims for RBC transfusions over an 8-week period consisting of the current and preceding 7 weeks. Patients were categorized as TD if they had ≥2 weeks with a claim for RBC transfusion(s), with any two claims separated by at least two weeks. For example, a patient who received RBC transfusions during weeks 1, 2, and 4 would be considered transfusion-dependent, but a patient who received RBC transfusions only during weeks 1 and 2 would not. Patients were classified as transfusion-independent (TI) during 8-week periods in which they received no transfusions. This algorithm was repeated for every week of follow-up from MDS diagnosis. As it would be expected that anemia management would be initiated on or before acceleration of transfusion need, patients with claims for ESAs prior to TD (the look-back period) were included (Fig. 1).

The primary study endpoint was achievement of TI. The observation period for the study began the first week in which an RBC transfusion defining TD occurred and ended at the earliest of the following: (1) achievement of TI, or censoring at (2) week 52, (3) 4 weeks prior to death, or (4) December 31, 2007 (Fig. 1).

2.3. ESA utilization measures and covariates

ESA utilization was calculated from weekly indicators of claims for an ESA product. Three variables were created from the weekly ESA claims measures: (1) the time from the beginning of TD to first observed ESA, (2) use of epoetin alfa, darbepoetin, or both; and (3) duration of ESA use, calculated by summing the weeks an ESA was received. We also characterized patients (yes/no) based on whether they had a claim for a serum erythropoietin determination, or any of the following while TD: G-CSF, hypomethylating agents (azacitidine or decitabine), or chemotherapy. We classified patients into lower-risk [refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia or MDS with del(5q)], higher-risk (refractory anemia with excess blasts), therapy-related MDS, and MDS not otherwise specified (NOS). Demographic characteristics were abstracted from the SEER database; comorbidities were captured from diagnoses on claims.

2.4. Statistical analysis

The distribution of clinical characteristics during the study period and study covariates were compared between patients who did or did not achieve TI using Chi-square tests. Kaplan–Meier life tables and survival curves were constructed to illustrate the association between ESA utilization measures and study outcome. Differences by ESA utilization were tested for statistical significance ($p < 0.05$) using the log rank test. Cox proportional hazards models were used to calculate hazard ratios (HR) for the study outcome, adjusting for covariates. Models examined the impact of choice of agent (epoetin alfa versus darbepoetin) and number of weeks of ESA use on the study outcome. As we did not expect a linear response between duration and likelihood of response, we grouped the ESA duration values into 8-week ranges. They included a variable to adjust for the time to initiation of ESA therapy following TD onset.

3. Results

A total of 8312 patients in the linked SEER-Medicare database had an MDS diagnosis. Among them, 2024 had at least one TD episode. Within this group, 610 received ESAs while TD and comprise the study cohort. Patient characteristics are summarized in Table 1. The average age was 78.2 years (SD ± 7.78) and 56.9% were male. The majority (91.3%) were classified as "white" race. There was an approximately equal distribution of higher- and lower-risk MDS patients (25.1% and 27.9%, respectively), while 47.1% were classified as MDS-NOS or therapy-related MDS and could not be assigned a risk category. Comorbidities were common in this older population, particularly ischemic heart disease (35.7%), chronic obstructive pulmonary disease (COPD, 19.8%), and diabetes mellitus (17.5%). Among the 610 patients, 239 (47.4%) received less than 8 weeks of ESA therapy, 198 (32.5%) 8–15 weeks, 87 (14.3%) 16–31 weeks, and 36 (5.9%) more than 32 weeks until TI or censoring (Table 2). Most patients (79.5%) received epoetin alfa, while 12.1% received darbepoetin and 8.4% received both.

Table 1
Patient characteristics ($N = 610$).

Characteristics	N	%
Age (years)		
<65	16	2.6
65–74	160	26.2
75–84	318	52.1
85+	116	19.0
Sex		
Male	347	56.9
Female	263	43.1
Race		
White	557	91.3
Black	17	2.8
Other	36	5.9
MDS risk category		
Low-risk	170	27.9
High-risk	153	25.1
Risk not specified	287	47.1
Comorbidities		
Congestive heart failure	87	14.3
Ischemic heart disease	218	35.7
Peripheral vascular disease	39	6.4
Cerebrovascular disease	30	4.9
Myocardial infarction	32	5.3
Diabetes or diabetes with complications	107	17.5
Chronic obstructive pulmonary disease	121	19.8
Rheumatologic disease	20	3.3
Depression or schizophrenia	38	6.2
Alzheimer's disease	30	4.9
Ulcer	15	2.5

Low- risk (RA, RARS, RCMD, 5q del); High- risk (RAEB); Risk not specified (Therapy-related MDS and MDS, NOS)

The median time from beginning of TD to first observed ESA was 4 weeks for all patients (data not shown), and there was no difference between patients receiving epoetin alfa and darbepoetin. TI was achieved in 210 (34.4%) patients, and the median time from ESA initiation to TI was 13 weeks. Among darbepoetin users, 47% (35/74) achieved TI, compared to 33.6% (163/485) of epoetin alfa users. Among the entire population, ESAs were administered an average of 11.0 (SD ± 10.43) weeks until TI or censoring. Among patients who achieved TI, 50% achieved TI after <8 weeks of ESA, 36.7% after 8–15 weeks and 13.4% after receiving more than 15 weeks (Table 2). Patients who achieved TI or were censored within less than 8 weeks of ESA use had the fastest median time to TI and the greatest likelihood of achieving TI in the hazard model after adjusting for age, sex, race, MDS risk category, time to ESA initiation and concurrent use of other therapies (Fig. 2, Table 3). Using this group as a comparator, the HR for achieving TI was 0.64 for patients receiving 8–15 weeks, 0.25 for patients receiving 16–31 weeks, and 0.10 for patients receiving more than 31 weeks ($p < 0.01$ for each, Table 3). Longer time from TD to initiation of ESA (HR 0.96 per week, 95% CI 0.94–0.99) predicted for lower rates of TI.

When patients who received both epoetin alfa and darbepoetin were excluded from the multivariable analysis, the results did not change substantially (Table 3). Using this model, 198 patients