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Patterns of erythropoiesis-stimulating agent use among Medicare beneficiaries with myelodysplastic syndromes and consistency with clinical guidelines

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Abstract

Erythropoiesis-stimulating agents (ESA) are used commonly to reduce symptomatic anemia in patients with myelodysplastic syndromes (MDS). We assessed population-based patterns of ESA use relative to treatment guidelines using data from the Surveillance, Epidemiology, and End Results (SEER) registries, with linked Medicare claims providing detailed treatment data from 2001 through 2005.

The study found widespread use (62%) of ESA in Medicare beneficiaries with MDS. Similar ESA use rates regardless of risk status, low frequency (45%) of serum erythropoietin determination prior to ESA initiation, and high prevalence (60.4%) of short-duration ESA episodes suggest clinically important discrepancies between actual practice and guideline-recommended therapy.

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Authors' Contribution

A.J.D., M.R.B., and S.D.G. provided the conception and design of the study. A.J.D., S.R.W., M.R.B., X.K., F.H., A.Z., S.D.G. were involved in analysis and interpretation of data. A.J.D. drafted the article. S.R.W., M.R.B., X.K., F.H., A.Z., S.D.G. revised the article critically for important intellectual content. A.J.D., S.R.W., M.R.B., X.K., F.H., A.Z., S.D.G. gave final approval of the article to be submitted.

Disclaimer

This article was prepared while A.J.D. was employed at University of Maryland Baltimore. The opinions expressed in this article are the author's own and do not reflect the view of the Agency for Healthcare Research and Quality, the Department of Health and Human Services, or the United States government.

Conflict of Interest

S.D.G. and A.J.D. owned Celgene stock until 12/2011. A.J.D. received additional funding from GlaxoSmithKline, Novartis, and Celgene until 8/2012. M.R.B. receives research funding from Novartis and Celgene. Other authors have no relevant conflict of interests to disclose.

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Keywords

Erythropoiesis-stimulating agent; myelodysplastic syndrome; guideline adherence; supportive care; Medicare

Introduction

Myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell neoplasms characterized by ineffective hematopoiesis. Approximately 80% of MDS patients experience symptomatic anemia. Supportive care to address this problem is an important goal in clinical management of MDS patients [1], and particularly those with lower-risk MDS, defined by refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD) or MDS with del(5q) subtypes [2] in the World Health Organization (WHO) classification, or by low or intermediate-1 risk scores in the International Prognostic Scoring System (IPSS) [3]. Erythropoiesis-stimulating agents (ESAs: erythropoietin- α , darbepoietin) [4] are a key component of the strategy for improving anemia and reducing dependence on red blood cell (RBC) transfusions. Clinical trial results indicate that approximately 40% of selected patients have a clinically meaningful hemoglobin response to ESAs, with a median two-year response [5–7].

ESA use in MDS is widespread; recent estimates suggest that 60% of MDS patients received ESAs [8]. To encourage evidence-based use of ESAs in MDS management, guidelines were developed by the National Comprehensive Cancer Network (NCCN) [9], with parallel statements by the Italian Society of Hematology [10] and the United Kingdom (UK) MDS Guidelines Group [11]. Key elements from all three sets of guidelines spanning the period from 2001–2006 are summarized in Appendix Table 1. The NCCN guidelines include comprehensive recommendations based on available Phase II and III trial results. During the study period, ESAs were recommended for anemia management in patients with lower-risk MDS with serum erythropoietin (EPO) concentrations < 500 IU/mL [12,13]. As improvements in hemoglobin are usually noted 6 to 8 weeks after initiation of an adequate dose of ESA, a minimum 8-week therapeutic trial was considered to be indicated. Moreover, it should be noted that ESA doses found to impact the anemia of MDS are substantially higher than those used in chronic renal insufficiency [14]. The addition of granulocyte colony-stimulating factor (G-CSF), thought to synergize with ESA in producing an erythropoietic effect in MDS patients, is suggested for patients who do not manifest a response to ESA [12,13]. A joint ESA-G-CSF regimen is recommended for patients with RARS, as they tend not to respond to ESA alone [13]. The NCCN guidelines defined ESA treatment failure by lack of hemoglobin increase by 1.5 gm/dL or decreased transfusion need following 8 weeks of treatment, but this definition was not incorporated until 2011 [9].

Information is not available concerning the extent to which ESA use for MDS is consistent with clinical guidelines. Practices inconsistent with guideline recommendations may include failure to target therapy to patients most likely to respond, defined by lower-risk MDS and low serum erythropoietin level, prescription of therapy of insufficient duration, and/or continuation of therapy despite treatment failure. ESAs are not without risks and are expensive to third-party payers and to patients who must cover a portion or all of the expense [8,15]. The lack of information on treatment risks specific to MDS patients makes it difficult to weigh the benefits to risks of continuing therapy in the absence of a clear clinical response.

In this study we compared patterns of ESA use to those indicated by the NCCN treatment guidelines, among MDS patients diagnosed from 2001 through 2005. Although not binding,

clinical guidelines provide an important metric against which appropriateness and quality of care can be measured. Moreover, understanding the dimensions along which guideline adherence may be particularly problematic may help to design interventions to improve adherence or to revise the guidelines.

Materials and Methods

Design Overview

This population-based observational study used administrative tumor registry and claims data to operationalize selected indicators of care management. These measures were compared to published treatment guidelines.

Data and Study Cohort

Patients were identified from the Surveillance Epidemiology and End Results (SEER) database, which aggregates data from 17 regional and state cancer registries, including information on cancer site, histology, diagnosis month, and vital status. For Medicare beneficiaries, SEER data from 16 registries are matched to Medicare enrollment and claims files [16]. Census tract-level demographic measures (e.g. income, education) supplement the demographic information from SEER and Medicare. Medicare Parts A and B claims provide detailed service-level information for covered services or drugs, identified through Healthcare Common Procedure Coding System (HCPCS) or National Drug Codes (NDC). Part B claims capture drugs administered by infusion or injection in a physician's office or outpatient setting, but not prescription medications covered more recently through Medicare Part D.

The sample included MDS cases newly reported between 2001 and 2005, with claims from 2000 through 2007. SEER reports the WHO classification system, using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) including 9980 (RA), 9982 (RARS), 9983 [refractory anemia with excess blasts (RAEB)], 9985 (RCMD), 9986 [MDS with del(5q)], 9987 [therapy-related MDS (t-MDS)], and 9989 [MDS, not otherwise specified (NOS)]. Approximately 87% of SEER-reported MDS cases have pathologic confirmation [17]. We used the SEER indicators to classify patients into lower-risk [RA, RARS, RCMD or MDS with del(5q)], higher-risk MDS (RAEB), therapy-related MDS (t-MDS), and MDS NOS.

Patients were excluded if they had incomplete information concerning diagnosis or death date; or any period without Medicare Parts A and B or with Medicare Advantage enrollment during the 12 months prior to, or any time after, diagnosis. These exclusions were necessary to ensure completeness of Medicare claims records. We excluded patients with a history of chronic renal failure or who received dialysis, as these patients may receive ESAs associated with their renal failure, which involves distinct patterns and doses.

Measurement of key variables

We created a longitudinal person-week file that summarized treatments and other services administered each week from diagnosis through death or censoring at the end of the study period. Each weekly observation included indicators for serum erythropoietin level determination, ESA administration, G-CSF, other treatments, and transfusions. Indicators were used to create ESA episodes and weekly measures of transfusion status. ESA episodes begin with the first week ESAs were used after MDS diagnosis. Episodes continued until a treatment gap of minimum three (epoetin-alfa) or six (darbepoetin) weeks, to account for longer activity of darbepoietin. Episode length was counted from the first through last week (epoetin-alfa) or the last week plus one (darbepoetin). Subsequent episodes were counted

using the same algorithm. We determined the transfusion status each week by examining the number and timing of transfusions in the current and preceding 7 weeks. Each week patients were designated as either transfusion-naïve (TN), -user (TU), -dependent (TD), or -independent (TI). TD required at least two of the previous 8 weeks with transfusions, with at least two weeks between them. TU required at least one transfusion, but not meeting the criteria for TD. Patients without transfusions in the 8-week period were designated as either TN if they had no prior transfusions, or TI if they had had prior transfusion use. Appendix Figure 1 illustrates the measurement of transfusion status. Although most measures focus on ESA use initiated after MDS diagnosis, we used claims from the period prior to MDS diagnosis to identify prior ESA use, and/or to complete measures of transfusion status.

Using the measures of transfusion status, diagnostic tests, and treatments over time, we operationalized five MDS management practices that could be measured reliably from the tumor registry data and/or claims data and compared to guidelines.

1. Targeting of ESA use to lower-risk MDS patients. In this analysis we compared ESA use rates by MDS risk group.
2. Serum EPO level to evaluate potential responsiveness to ESAs. We determined whether the patient ever had an EPO level determined and whether the EPO level was determined prior to ESA initiation.
3. Use of concurrent ESA and G-CSF as initial therapy for patients with RARS subtype. We determined whether G-CSF was received during any week of the first ESA episode and compared use rates across WHO categories.
4. Minimum 8-week ESA episode. We calculated the distribution of episode lengths, and then constructed measures at the patient level for the total number of episodes and number of episodes with length ≥ 8 weeks. Episodes of 8 or more weeks are deemed to be of adequate length to generate a therapeutic response; referred to as “therapeutic episodes.”
5. Discontinuation of ESA when there was evidence of treatment failure. To assess this, we measured duration of concurrent ESA use and TD status. Among patients who initiated ESA treatment when TN or TI, we considered progression to TD as an indicator of treatment failure, and measured the weeks of continued ESA use after TD progression. For patients who initiated ESA while TD, we expected ESA therapy to persist for at least 8 weeks, and then be escalated, switched, augmented with G-CSF, or ultimately discontinued if TD persisted. We considered concurrent ESA use with persistent TD status after 12 weeks as an indicator of potential treatment failure.

Statistical Analysis

Univariate and bivariate techniques were used to describe patterns of ESA use for the full MDS sample, with stratification by MDS risk group, and type and timing of ESA use. A two sided chi-squared or t-test with $\alpha = 0.05$ was used to compare proportions across MDS category or ESA type. Analyses used SAS 9.2 (SAS, Cary, NC) or Stata 10 (Statacorp., College Station, TX.). The project was approved by the University of Maryland Baltimore Institutional Review Board.

Results

The sample included 6,588 patients with MDS. 88.5% were white, and 47.1% were over age 80; 34.6% were lower-risk, 13.7% higher-risk, 1.4% t-MDS and 50.4% MDS-NOS. Additional sample characteristics are reported in Appendix Table 2 (online only). 4,257

patients, or 62.4%, had at least one episode of ESA use after their MDS diagnosis (Table 1). Among users, most received only erythropoietin-alfa (61.9%) or both agents (25.8%), while only 12.3% received only darbepoetin. Estimates stratified by MDS risk group indicate almost identical ESA use rates, at 66.5% and 66.4%, in lower- and higher-risk groups.

Among patients initiating ESA therapy after their MDS diagnosis date, only 45.0% had an EPO determination, and only 31.9% had an EPO level measured within 12 weeks prior to initiating ESA (Table 2). Of those not receiving ESAs, 15.6% had an EPO level measured. EPO determination rates were higher for lower-risk compared to higher-risk MDS, at 48.5% and 42.8%, respectively.

Overall, 13.8% of MDS patients received concurrent G-CSF during their initial ESA episode (Table 3). The rate was 10.6% for the RARS subtype, with higher rates observed among higher risk/RAEB (21.8%), RCMD (19.0%) and del5q (16.2%) patients ($p < 0.01$). Duration of concurrent ESA and G-CSF use was longer (29.5 weeks) in RARS compared with 11.4 weeks in RAEB, 16.1 week for RA, 13.6 weeks for RCMD and 11.4 weeks for del5q.

Patients initiating ESA use after MDS diagnosis experienced 11,755 distinct episodes of ESA treatment, representing a mean of 3.5 [median, 2] treatment episodes per patient. Overall, 60.4% of ESA treatment episodes were < 8 weeks in length (Figure 1A). Among ESA-treated patients, only 25.3% were treated with a single therapeutic episode, while 28.0% received only non-therapeutic-length episodes (Figure 1B).

Most patients (55.4%) were TN at the time of ESA initiation, with an additional 5.8% having reverted to TI. Among this subgroup of patients ($N = 2,517$; 61.2%), 12.8% developed TD during the ESA episode. Once patients became TD, there was a mean 14.1-week period of concurrent TD and ESA use (95% CI 12.0–16.2), with 37.3% of patients who became TD receiving 12 or more additional weeks of ESA therapy, while 15.8% received 24 or more weeks (Table 4).

Among the 10.8% of patients who initiated their first ESA episode while TD, the ESA episode lasted a mean of 17.4 weeks (95% CI: 15.0–19.8), with concurrent ESA use and TD lasting a mean of 10.4 weeks (95% CI: 9.0–11.9); 23.5% of patients received 12 or more weeks of ESA while TD. Despite the fact that 66.8% remained TD at the end of the episode, 36.1% of those patients went on to receive a subsequent ESA episode (Table 4).

Discussion

This study examined ESA treatment patterns in a large, population-based sample of Medicare beneficiaries diagnosed with MDS between 2001–2005. Longitudinal analyses described not only whether patients received ESAs, but the patterns over time and the relationship to diagnostic evaluation and transfusion use. Using the NCCN guidelines as a standard for appropriate care, we observed a frequent lack of concordance between practice and guidelines. Patients were frequently not targeted for therapy based on risk status, as evidenced by high rates of use across all risk groups, or on the likelihood of achieving response, as evidenced by frequent lack of measurement of serum EPO levels prior to ESA use. Duration of therapy was not consistent with guidelines, as a majority of episodes of ESA therapy were not of sufficient length to produce treatment responses. The pattern of brief episodes affected a substantial proportion of patients, with over one-fourth of users never receiving a therapeutic-length episode. Additionally, we found evidence that therapy is continued for prolonged periods despite progression to transfusion dependence, however this affected a relatively small proportion of treated patients.

It was expected that ESA use would be more common in patients with lower-risk, compared to higher-risk, MDS, but this was not observed. It is unknown whether this pattern has changed over time. With the availability of other agents more appropriate for initial therapy of higher-risk MDS, including azacitidine and decitabine (approved by the US Food and Drug Administration in 2004 and 2006, respectively) we would expect lower ESA use rates. Only 7% of patients in our cohort had any evidence of receiving either of these drugs during the observation period, suggesting that they played a minor role, if any, on ESA initiation. Lenalidomide, a disease modifying therapy indicated for lower-risk MDS with a 5q deletion, entered the market in December 2005, and may also have affected ESA use. We did not have access to prescription drug claims, thus could not assess frequency of use in our cohort.

It is not clear why clinicians did not commonly measure serum EPO levels. All patients who received ESAs should have had an EPO level measured prior to initiating ESA therapy, and failure to measure the level is a clear signal that such information was not used to target patients. Claims data during this period do not provide information on the actual laboratory result, so we cannot determine whether the information was used appropriately in the cases in which it was obtained.

The majority of ESA episodes (60%) were initiated and discontinued without sufficient duration to induce treatment response, and over one fourth of ESA users never had a therapeutic-length episode. Potential explanations for this early discontinuation include treatment-related adverse events, but these are not documented in the literature for MDS patients [18]. Alternatively, patient access barriers associated with lack of supplemental insurance coverage and impaired mobility may interfere with continuation of therapy. In related research, we found that poor socioeconomic status and mobility limitations were key predictors of failure to receive ESAs, and failure to receive a therapeutic length episode among ESA users [19]. Alternatively, physicians may not have been well informed about the duration of ESA treatment necessary to produce response.

Among patients who initiated ESA treatment when TN or TI, we expected ESA to be discontinued soon after progression to TD. While this was true for most patients, there was a small group for whom therapy was continued for an extended period. While it is possible that there were dose adjustments, agent switches (erythropoietin alfa to darbepoietin) or the addition of G-CSF, a post-hoc exploration of those events indicated that they were not common.

The gap between guidelines and practice reported in this study is consistent with some, but not all, studies examining adherence to guidelines for use of ESAs and CSFs in cancer patients. Several studies have examined adherence to guidelines for target hemoglobin levels, finding that relatively little ESA use is for patients with elevated levels [20–22]. In contrast, a recently published study examined use of ESAs for chemotherapy-induced anemia [23], finding that patients commonly received therapy that was either too brief to have therapeutic effect or was continued for extended periods once chemotherapy was completed.

There are several important limitations to our study. Concern has been expressed that SEER may under-report MDS cases managed primarily in the community, which are likely to be less advanced. However, other studies not based on SEER-Medicare suggest similar rates of ESA use [8]. It is not clear that adherence to guidelines would be particularly stronger in community practice, hence the results from this study can be considered a conservative estimate of the gap between guidelines and practice. Other limitations associated with the data include a concern for under-reporting of services provided, both diagnostic testing (e.g. EPO levels) and treatments. Validation studies have established the high reporting rates for

chemotherapy treatment [24], and we anticipate similar rates for ESAs. We note that a portion of beneficiaries were exposed to various types of chemotherapy not generally used to treat MDS or AML. We were unable to determine whether ESA use patterns reflected treatment of chemotherapy induced anemia rather than anemia associated with MDS. The large proportion of patients designated MDS-NOS and the lack of clinical laboratory values on claims data limited our ability to examine adherence to the NCCN guidelines. The data lack information regarding patient preferences and clinician intent, which, if available, might provide explanations for some of the observed patterns. However, as the purpose of this study is to document practice patterns, rather than to explain them or detail interventions to improve adherence, these limitations provide a direction for future research. Our results reflect patterns of practice within the context of Medicare coverage and reimbursement policies, and hence, may not be generalizable to MDS patients not enrolled in Medicare.

Overall high ESA use rates across risk groups may reflect a variety of pressures on physicians managing MDS patients during the time period reflected in our data. Patients may have pressured physicians to ignore recommendations for various types of therapeutic targeting. Patients may have been encouraged by “direct to consumer” advertisements that emphasized improvements in quality of life [25, 26]. Alternatively, the lack of effective disease-modifying therapies for MDS until the market entry of azacitidine in 2004 may have been a factor. While difficult to assess, it is important to recognize that physicians also faced financial incentives to use ESAs [27, 28], through both Medicare reimbursements that did not reflect physician purchase prices, and receipt of rebates from pharmaceutical companies. In related research on ESA use in MDS and for chemotherapy-induced anemia, physician characteristics such as practice venue were significant predictors of use, which is consistent with the idea that financial incentives may play a role [19,23].

Finally, concerns about the safety of ESAs were raised in several studies published beginning in 2003. Associations were found between ESA use in cancer patients and venous thromboembolic events, tumor progression and reduced overall survival [29–33]. In 2007–2008, the U.S. Food and Drug Administration (FDA) issued safety alerts and required pharmaceutical companies to add safety warnings to ESA labels. MDS was not referenced in the FDA warnings, and there is relatively little information on long-term ESA administration in MDS patients [34, 35]. Nevertheless, it is possible that the safety warnings may have affected ESA use in MDS patients.

In this study, we found that much ESA use in the years 2001–2007 was not consistent with expert recommendations disseminated via the NCCN guidelines. The current results suggest that stricter adherence to guidelines would decrease inappropriate use of ESAs, presumably substantially decreasing costs associated with this therapy. During the latter half of the decade, ESA use in MDS may have been affected by the availability of other agents to treat higher-risk MDS, as well as by the FDA safety warnings, a National Coverage Determination concerning ESA use for chemotherapy induced anemia issued by the Centers for Medicare and Medicaid Services in 2007 [36], and the implementation of a Risk Evaluation and Management Strategy program by the FDA in 2010 [37]. The results of the current study underscore the need for ongoing assessment of appropriateness of ESA use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Melchert M, List AF. Management of RBC-transfusion dependence. *Hematology Am Soc Hematol Educ Program*. 2007;398–404. [PubMed: 18024657]
2. Howe RB, Porwit-MacDonald A, Wanat R, Tehranchi R, Hellström-Lindberg E. The WHO classification of MDS does make a difference. *Blood*. 2004; 103:3265–3270. [PubMed: 14684416]
3. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997; 89:2079–2088. [PubMed: 9058730]
4. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. [Accessed at on 5 September 2011.] Drugs@FDA drug information database. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>
5. Hellström-Lindberg E, Ahlgren T, Beguin Y, Carlsson M, Carneskog J, Dahl IM, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: Results from a randomized phase II study and long-term follow-up of 71 patients. *Blood*. 1998; 92:68–75. [PubMed: 9639501]
6. Negrin R, Stein R, Doherty K, Cornwell J, Vardiman J, Krantz S, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. *Blood*. 1996; 87:4076–4081. [PubMed: 8639764]
7. Golshayan AR, Jin T, Maciejewski J, Fu AZ, Bershady B, Kattan MW, et al. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes. *Br J Haematol*. 2007; 137:125–132.
8. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. *J Natl Cancer Inst*. 2008; 100:1542–1551. [PubMed: 18957672]
9. National Comprehensive Cancer Network. [Accessed at on 5 September 2011] NCCN Guidelines™ version 2.2011 updates myelodysplastic syndromes. http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf Archived versions of the guidelines from 2001 and 2006 were obtained from the NCCN
10. Alessandrino EP, Amadori S, Barosi G, Cazzola M, Grossi A, Liberato LN, et al. Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology. *Haematologica*. 2002; 87:1286–1306. [PubMed: 12495903]
11. Bowen D, Culligan D, Jowitt S, Kelsey S, Mufti G, Oscier D, et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. *Br J Haematol*. 2003; 120:187–200. [PubMed: 12542475]
12. Jädersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol*. 2008; 26:3607–3613. [PubMed: 18559873]
13. Hellström-Lindberg E, Gulbrandsen N, Lindberg G, Ahlgren T, Dahl IM, Dybedal I, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol*. 2003; 120:1037–1046. [PubMed: 12648074]

14. Oliva EN, Nobile F, Alimena G, Specchia G, Danova M, Rovati B, et al. Darbepoetin alfa for the treatment of anemia associated with myelodysplastic syndromes: efficacy and quality of life. *Leuk Lymphoma*. 2010; 51:1007–1014. [PubMed: 20367566]
15. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med*. 2009; 360:626–633. [PubMed: 19176475]
16. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002; 40(Suppl IV):IV-3–IV-18.
17. Rollison DE, Howlader N, Smith MT, Strom SS, Merritt WD, Ries LA, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001–2004, using data from the NAACCR and SEER programs. *Blood*. 2008; 112:45–52. [PubMed: 18443215]
18. Weiss Smith S, Sato M, Gore SD, Baer MR, Ke X, McNally D, et al. Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes. *Haematologica*. 2012; 97:15–20. [PubMed: 22102702]
19. Davidoff AJ, Weiss Smith S, Baer MR, Ke X, Bierenbaum JM, Hendrick F, et al. Patient and physician characteristics associated with erythropoiesis-stimulating agent use in patients with myelodysplastic syndromes. *Haematologica*. 2012; 97:128–132.
20. Hess G, Hill J, Clough J, Hulnick S, Nordyke RJ. Utilization of darbepoetin alfa in relation to cancer patients' hemoglobin levels. *Curr Med Res Opin*. 2008; 24:815–819. [PubMed: 18257979]
21. Nordstrom BL, Luo W, Fraeman K, Whyte JL, Nordyke RJ. Use of erythropoiesis-stimulating agents among chemotherapy patients with hemoglobin exceeding 12 grams per deciliter. *J Manag Care Pharm*. 2008; 14:858–869. [PubMed: 19006442]
22. Luo W, Nordstrom BL, Fraeman K, Nordyke R, Ranganathan G, Linz HE, et al. Adherence to guidelines for use of erythropoiesis-stimulating agents in patients with chemotherapy-induced anemia: results of a retrospective study of an electronic medical-records database in the United States, 2002–2006. *Clin Ther*. 2008; 30:2423–2435. [PubMed: 19167601]
23. Wright JD, Neugut AI, Wilde ET, Buono DL, Malin J, Tsai WY, et al. Physician characteristics and variability of erythropoiesis-stimulating agent use among Medicare patients with cancer. *J Clin Oncol*. 2011; 29:3408–3418. [PubMed: 21810679]
24. Warren JL, Harlan LC, Fahey A, Virnig BA, Freeman JL, Klabunde CN, et al. Utility of the SEER-Medicare data to identify chemotherapy use. *Med Care*. 2002; 40(suppl IV):IV-55–61.
25. MedPage Today. [Accessed at on 5 September 2011.] Anemia Drugs' Marketing in Congressional Crosshairs. <http://www.medpagetoday.com/ProductAlert/Prescriptions/8991>
26. Abel GA, Penson RT, Joffe S, Schapira L, Chabner BA, Lynch TJ Jr. Direct-to-consumer advertising in oncology. *Oncologist*. 2006; 11:217–226. [PubMed: 16476842]
27. Adams JR, Elting LS, Lyman GH, George JN, Lembersky BC, Armitage JO, et al. Use of erythropoietin in cancer patients: assessment of oncologists' practice patterns in the United States and other countries. *Am J Med*. 2004; 116:28–34. [PubMed: 14706663]
28. Cotter D, Thamer M, Narasimhan K, Zhang Y, Bullock K. Translating epoetin research into practice: the role of government and the use of scientific evidence. *Health Aff (Millwood)*. 2006; 25:1249–1259. [PubMed: 16966720]
29. Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas S, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol*. 2005; 23:5960–5972. [PubMed: 16087945]
30. Henke M, Laszig R, Rübe C, Schäfer U, Haase KD, Schilcher B, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2003; 362:1255–1260. [PubMed: 14575968]
31. Danish Head and Neck Cancer Group. [Accessed at on 5 September 2011.] Interim Analysis of DAHANCA 10, study of the importance of Novel Erythropoiesis Stimulating Protein (Aranesp®) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck. http://www.dahanca.dk/get_media_file.php?mediaid=125

32. Ross SD, Allen IE, Henry DH, Seaman C, Sercus B, Goodnough LT. Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature. *Clin Ther.* 2006; 28:801–831. [PubMed: 16860166]
33. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA.* 2008; 299:914–924. [PubMed: 18314434]
34. Steensma DP. Erythropoiesis-stimulating agents are effective in myelodysplastic syndromes, but are they safe? *Am J Hematol.* 2009; 84:3–5. [PubMed: 19037863]
35. Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, et al. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). *Blood.* 2009; 114:2393–2400. [PubMed: 19564636]
36. Centers for Medicare and Medicaid Services. [Accessed at on 15 November 2012.] National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21). <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=322&ncdver=1&bc=AAAAQAAAAAAAA&>
37. U.S. Food and Drug Administration. [Accessed at on 5 September 2011.] FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen and Aranesp. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm>

Figure 1. Duration of erythropoiesis stimulating agent episodes and distribution of myelodysplastic syndrome patients by number and duration of episodes^{*,†}

Figure 1A

Distribution of MDS patients by number, duration of ESA episodes

- All episodes < 8 weeks
- ▒ One episode >= 8 weeks
- Multiple episodes >= 8 weeks
- Multiple episodes, mixed length

Figure 1B

Distribution of ESA episodes by duration, agent

- < 8 weeks
- ▒ 8-15 weeks

■ 16–31 weeks

■ 32–63 weeks

■ 64+ weeks

* Source: SEER-Medicare, cases from 2001–2005, claims from 2000–2007

† Abbreviations: ESA, erythropoiesis stimulating agents; SEER, Surveillance, Epidemiology and End Results

Table 1

Receipt of erythropoiesis stimulating agents (ESAs) among Medicare enrolled patients with myelodysplastic syndromes(MDS) ^{*,†,‡}

	All Risk Groups		Lower Risk		Higher Risk		Treatment Related or MDS Not Otherwise Specified	
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
N	6,588		2,276		904		3,408	
(%)	100.0		34.5		13.7		51.7	
ESA Use								
Any during pre- and/or post diagnosis obs period	64.6		68.5		67.9		61.2	
Pre-diagnosis only	2.2		2.0		1.6		2.5	
Post diagnosis	62.4		66.5		66.4		58.6	
Among ESA Users (N=4257) [‡]								
Erythropoietin-alfa only	61.9		56.5		66.9		64.5	
Darbepoetin alfa only	12.3		13.0		12.5		11.6	
Both agents	25.8		30.5		20.5		23.9	

^{*} Source: Analysis of SEER-Medicare cases from 2001–2005

[†] Note: Difference between lower and higher risk MDS patients significant at p<.001

[‡] Abbreviations: ESA erythropoiesis stimulating agents; MDS myelodysplastic syndromes; SEER Surveillance, Epidemiology and End Results

Table 2

Proportion of Medicare beneficiaries with myelodysplastic syndrome patients receiving serum erythropoietin determinations (EPO level) ^{*,†,‡}

	All Risk Groups		Lower Risk		Higher Risk		Treatment Related or MDS Not Otherwise Specified	
	(%)		(%)		(%)		(%)	
N	6,588		2,276		904		3,408	
(%)	100.0		34.5		13.7		51.7	
EPO level performed, any time during observation period								
Overall ***	33.0		37.9		32.6***		29.9	
Among ESA users (pre or post dxdt) **	42.6		46.1		41.0**		40.4	
Among non-users of ESA *	15.6		19.9		14.8*		13.4	
Among ESA users initiating ESA post MDS diagnosis only								
EPO level any time during observation period **	45.0		48.5		42.8**		42.8	
EPO level within 12 weeks prior to ESA initiation	31.9		33.9		30.6		30.7	

^{*} Source: Analysis of SEER-Medicare cases from 2001–2005

[†] Note: Difference between lower and higher risk MDS patients significant at ^{*}p<.10; ^{**}p<.05; ^{***}p<.01

[‡] Abbreviations: EPO, serum erythropoietin; MDS, myelodysplastic syndromes; ESA, erythropoiesis stimulating agents; dxdt, diagnosis date; SEER, Surveillance, Epidemiology and End Results

Table 3

Concurrent initial use of erythropoiesis stimulating agents and granulocyte colony-stimulating factor in Medicare beneficiaries with myelodysplastic syndromes ^{*,†,‡}

	G-CSF use during first ESA episode			G-CSF use during first ESA episode – by individual WHO category				
	All Risk Groups	Lower- Risk	Higher- Risk	Treatment-Related or MDS Not Otherwise Specified	RA	RARS	RCMD	del5q
N	6,588	2,276	904	3,408	1,090	780	289	117
% with concurrent G-CSF & ESA use	13.8	11.0	21.8	13.5	8.5	10.6	19.0	16.2
Mean weeks with concurrent G-CSF & ESA use, among those with concurrent use (SE)	15.77 (0.82)	19.65 (1.95)	11.42 (1.14)	15.54 (1.11)	16.13 (2.51)	29.49 (4.60)	13.60 (2.87)	11.37 (2.88)

* Source: Analysis of SEER-Medicare cases from 2001–2005, claims from 2000–2007

† Note: All differences between lower- and higher-risk MDS patients and across lower-risk MDS categories significant at p<0.01

‡ Abbreviations: ESA=erythropoiesis-stimulating agents; G-CSF= granulocyte colony-stimulating factor; MDS= myelodysplastic syndromes; RA= refractory anemia; RARS=refractory anemia with ringed sideroblasts; RCMD=refractory cytopenia with multilineage dysplasia; del5q = deletion 5q syndrome; SEER=Surveillance, Epidemiology and End Results

Prolonged use of erythropoiesis-stimulating agents concurrent with transfusion dependence in patients with myelodysplastic syndromes ^{*,†}

Table 4

	Transfusion Status at ESA Initiation (1st Episode)	
	Naïve or Independent	Dependent
N (%) of patients with ESA use	2,517 61.2%	446 10.8%
N (%) of patients who transitioned to TD during ESA episode	322 12.8%	NA
Among patients who initiated or transitioned to TD status		
Duration of ESA episode (weeks; mean, 95% CI)	51.8 (46.6–57.0)	17.4 (15.0–19.8)
Duration of concurrent ESA & TD		
Mean, 95% CI (weeks)	14.1 (12.0–16.2)	10.4 (9.0–11.9)
% with >= 12 weeks	37.3%	23.5%
% with >= 24 weeks	15.8%	9.6%
Patient still TD at end of concurrent ESA & TD period	57.5%	66.8%
Patients who have subsequent ESA episode	40.4%	36.1%

^{*} Source: Analysis of SEER-Medicare cases from 2001–2005

[†] Abbreviations: ESA=erythropoiesis-stimulating agents; TD = transfusion dependent; TI= transfusion independent; TN=transfusion naïve; SEER=Surveillance, Epidemiology and End Results; NA=not applicable, patient already TD at ESA initiation.