Leukemia Research 60 (2017) 123–128

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

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

Christopher R. Cogle[a,*], Sheila R. Reddy[b], Eunice Chang[b], Elya Papoyan[b], Michael S. Broder[b], Michael McGuire[c], Gary Binder[d]

[a] Division of Hematology and Oncology, Department of Medicine, College of Medicine, University of Florida, 1600 SW Archer Rd, Box 100278, Gainesville, FL 32610, USA
[b] Partnership for Health Analytic Research, LLC, Beverly Hills, CA 90215, USA
[c] US HEOR Department, Celgene Corporation, 86 Morris Avenue, Summit, NJ 07901, USA
[d] Celgene Corporation, 86 Morris Avenue, Summit, NJ 07901, USA

ARTICLE INFO

Keywords:
MDS
Transfusion burden
Treatment timing

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

* Corresponding author.
E-mail addresses: christopher.cogle@medicine.ufl.edu (C.R. Cogle), srreddy@pharllc.com (S.R. Reddy), echang@pharllc.com (E. Chang), epapoyan@gmail.com (E. Papoyan), mbroder@pharllc.com (M.S. Broder), mmcguire@celgene.com (M. McGuire), garybinder@yahoo.com (G. Binder).

http://dx.doi.org/10.1016/j.leukres.2017.07.008
Received 21 April 2017; Received in revised form 12 July 2017; Accepted 31 July 2017
Available online 01 August 2017

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-

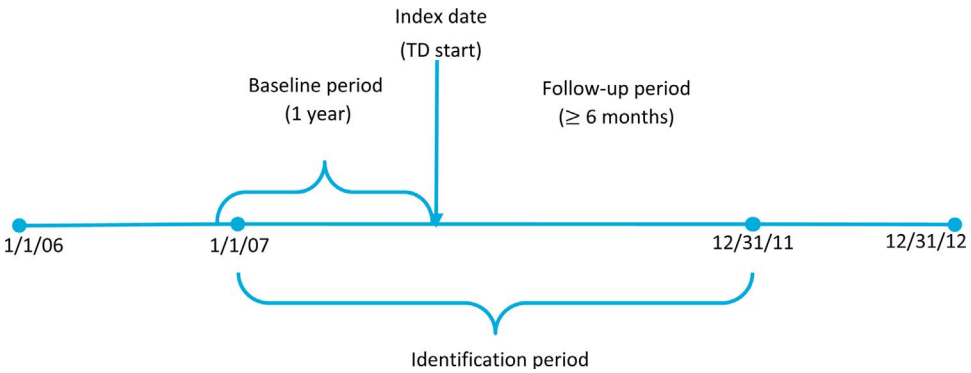

Fig. 1. Study time frame. Identification period: using SEER, we identified patients with MDS between 2007 and 2011 who became TD and were treated with azacitidine, decitabine, or lenalidomide (disease-modifying treatment). Index date: date of first transfusion within the 16-week period used to define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