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Research paper

Relationship between lenalidomide dose modification, duration of therapy, and long-term outcomes in patients with myelodysplastic syndromes

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ABSTRACT

Dose reductions or interruptions may be required to manage treatment-associated adverse events among patients with myelodysplastic syndromes (MDS) treated with lenalidomide; such modifications are recommended to sustain therapy and maximize treatment duration. The aim of this retrospective case-control study was to determine the relationship between lenalidomide dose modification (DM), duration of lenalidomide therapy (DOT), and patient outcomes in patients with MDS. Those patients with database follow-up > 20 months (n = 305) were more likely to have received erythropoiesis-stimulating agents (ESAs) ($P = 0.004$), had longer median DOT ($P < 0.001$), and higher rate of DM ($P < 0.001$) versus those with shorter follow-up (n = 306). Multivariate analysis indicated that lenalidomide DM (odds ratio [OR] 1.08) and prior ESA treatment (OR 2.40) were significantly associated with longer follow-up; transfusion dependence before lenalidomide initiation was associated with a significantly shorter follow-up (OR 0.60). These data suggest that effective management of lenalidomide treatment using dose reduction and/or delay is associated with longer DOT, which can improve patient outcomes.

1. Introduction

Myelodysplastic syndromes (MDS) are a complex and heterogeneous group of hematological malignancies, characterized by deficits in the proliferation, differentiation, and maturation of bone marrow stem cells [1]. Ineffective hematopoiesis is a hallmark of these malignancies and, in lower-risk patients, management of the resultant cytopenias (predominantly anemia) is difficult and is generally the primary focus of therapy [2].

Lenalidomide is approved in the USA for the treatment of anemia in patients with International Prognostic Scoring System (IPSS)-defined Low- or Intermediate-1-risk MDS who have the deletion 5q [del(5q)] abnormality, with or without additional chromosomal abnormalities [3]. Several clinical studies have demonstrated the efficacy of lenalidomide in patients with del(5q) MDS [4,5] and non-del(5q) [6,7]. In these studies, fewer patients with non-del(5q) MDS tend to respond to lenalidomide compared with patients with del(5q) disease (approximately 26% vs. 70–80%, respectively), but lenalidomide remains a viable therapeutic option for these patients [4–7]. Data from a large cohort of Medicare-enrolled patients with MDS have also demonstrated that the efficacy of lenalidomide in a real-world setting is similar to that observed in clinical trials [8].

Dose reductions and/or interruptions are often required to manage lenalidomide-associated adverse events. Such modifications are recommended to sustain therapy and maximize treatment duration allowing patients to achieve optimal clinical benefit [4,5,7,9,10]. In the pivotal MDS-003 trial of patients with del(5q) MDS, 80% of patients required dose interruption or reduction (median time: 22 days) and 34% of patients had a second dose interruption or reduction [4]. Additionally, in the MDS-005 trial of patients with non-del(5q) MDS, 39.4% of patients required a dose reduction or interruption in the lenalidomide arm, compared with 5.1% of patients in the placebo arm [7].

The aim of this study was to determine the relationship between lenalidomide dose modification, duration of lenalidomide therapy, and patient outcomes in patients with MDS.

Abbreviations: CCMC, Commercial Claims and Medicare; CCI, Charlson Comorbidity Index; del(5q), deletion 5q abnormality; DOT, duration of therapy; DM, dose modification; ESAs, erythropoiesis-stimulating agents; G-CSF, granulocyte colony-stimulating factor; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IPSS, International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndromes; MDS-CI, MDS-specific Comorbidity Index; OR, odds ratio; RBC, red blood cell; TD, transfusion-dependent

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2. Methods

2.1. Data source and study design

We conducted a retrospective case-control analysis of patients with MDS treated with lenalidomide using patient outcomes as the exposure variable.

Patients were stratified into case or control groups according to the time between index date and disenrollment (i.e., the duration of data available since lenalidomide initiation). As mortality data are generally unavailable in commercial claims databases, the date of insurance disenrollment was used as a proxy for survival; this approach has been used previously to approximate survival in similar insurance claims analyses of patients with cancer [11]. In the final study sample, the median time to disenrollment was 20 months, and this was used as the variable for stratification allowing for an equal number of patients in each comparator group.

The study design was chosen to address potential survivorship bias. Where patients without any evidence of dose modification could simply have been nonresponders, the current design includes these patients in both the case and control group. By virtue of their longer survival after the index date, patients in the case group had better outcomes than those in the control group. This analysis aimed to determine which key clinical and treatment characteristics differentiate the two patient groups and which factors increase the likelihood of a patient having improved outcomes.

The Truven Healthcare MarketScan® Commercial Claims and Medicare (CCMC) databases, which cover medical and drug claims data from > 100 million commercial and Medicare patients, were used as the data source for this analysis. The cutoff date for inclusion in the analysis was May 30, 2015.

2.2. Study population

Patients from the CCMC databases were included in the analysis if they had made at least one insurance claim for MDS (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 238.72–238.75) between October 1, 2006 and May 30, 2015. The index date was defined as the date of the first claim for lenalidomide.

The study population was further refined using the following inclusion criteria: patients were required to have made at least one inpatient or at least two outpatient claims associated with a primary or non-primary diagnosis of MDS (ICD-9-CM codes: 238.72–238.75) and to be aged ≥18 years at diagnosis (Fig. 1). Patients on lenalidomide were required to have received a prescription fill for at least two cycles (56-day supply, two claims) within 60 days of an MDS claim; the first fill was defined as the index date. To ensure data completeness, patients were required to have continual insurance coverage from 12 months before the index date until 6 months after. Patients were excluded from the analysis if they had more than two claims associated with a diagnosis of multiple myeloma (ICD-9-CM code: 203.0x) or lymphoma (ICD-9-CM code: 200–202). ICD-9-CM codes for acute myeloid leukemia were not investigated to determine whether patients evolved subsequent to the initial date of MDS coding. Clinical information was not available to stratify between patients with lower- and higher-risk MDS.

2.3. Outcome measures

The following variables were compared across case and control groups to identify which had a significant impact on patient outcomes or duration of lenalidomide therapy: age at MDS diagnosis, gender, duration of follow-up, US region, payer type, MDS type (based on ICD-9-CM code), time to initiation of lenalidomide treatment from MDS diagnosis, MDS therapies received prior to lenalidomide, incidence of cytopenias within 3 months of lenalidomide treatment, and red blood cell (RBC) transfusion dependence before initiation of lenalidomide treatment. Transfusion dependence was defined as evidence of a transfusion on at least 1 day during two consecutive 8-week periods and with a gap of no more than 56 days between transfusions.

The MDS treatments reviewed in the analysis were: erythropoiesis-stimulating agents (ESAs), granulocyte colony-stimulating factor (G-CSF), and the hypomethylating agents azacitadine and decitabine. All types of cytopenias were reviewed, including anemia, thrombocytopenia, neutropenia, and pancytopenia.

Disease burden was measured by the MDS-specific Comorbidity Index (MDS-CI) at treatment index using methods described by Della Porta et al. [12]. The Charlson Comorbidity Index (CCI) was based on the previous history of each patient as described by Charlson et al. and Deyo et al. [13,14].

Lenalidomide treatment-specific variables included starting dose, duration of therapy, occurrence and frequency of dose modification, and time to first dose modification. Dose modifications were identified when there was a change in the treatment strength between two consecutive claims or a significant delay/interruption in treatment (i.e., a gap between expected fill dates of more than 10 days but fewer than 60 days). Patients were considered to have discontinued therapy if the gap between treatments was more than 60 days.

2.4. Statistical methods

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), with a two-sided P value < 0.05 considered significant. Baseline demographics were summarized using descriptive statistics, and categorical variables were summarized with frequencies and proportions. Differences between case and control groups were

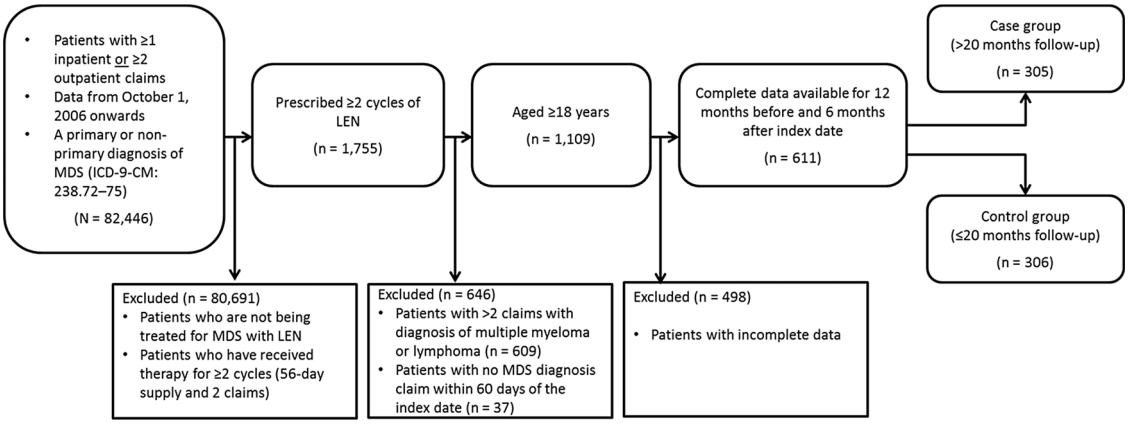

Fig. 1. Study attrition flow diagram. ICD-9-CM, The International Classification of Diseases, Ninth Revision, Clinical Modification; LEN, lenalidomide; MDS, myelodysplastic syndromes.