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Epidemiology of Myelodysplastic Syndromes

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Abstract

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematopoietic stem cell malignancies with significant morbidity and high mortality. The incidence of MDS increases markedly with age, and the disease is most prevalent in individuals who are white and male. It is conservatively estimated that >10,000 new cases of MDS occur in the United States annually, and that 60,000 individuals with MDS currently reside in the country. With an aging population and an improving awareness of the disease, the documented disease burden is expected to escalate in the near future. Recent studies have identified new or inconsistent etiologic factors that warrant further research. Given the poor survival of individuals with MDS, it is important to identify prognostic factors to better risk-stratify patients for more effective treatment. The relevance of different comorbidities to MDS prognosis and the potential interaction between various comorbidities represents an interesting area of research.

Keywords

Incidence; Myelodysplastic syndromes; Prevalence; Prognosis

For many years, myelodysplastic syndromes (MDS) were considered preleukemic conditions owing to a relatively high rate of disease progression to acute myeloid leukemia (AML). More recent research has suggested that MDS has a clonal nature. In 2000, the World Health Organization (WHO) changed the behavior code for MDS in the *International Classification of Diseases for Oncology* (ICD-O) from 1 (i.e., uncertain whether benign or malignant) to 3 (i.e., malignant).¹ Subsequently, in 2001 MDS became reportable to population-based cancer registries, such as the Surveillance, Epidemiology, and End Results (SEER) Program led by the US National Cancer Institute (NCI), which made it possible to obtain population-level data on MDS morbidity and mortality. The addition of MDS to cancer reporting represents an important step toward better describing the morbidity and mortality of the disease.

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INCIDENCE AND PREVALENCE

Incidence is defined as the rate at which new cases of a disease or condition occur. In 1995, the number of incident MDS cases in the United States was estimated to be around 1,500 annually.² Two other more recent studies that used newly available cancer registry data put the estimate at slightly >10,000 annually.^{3,4} A recent study based on Medicare claims reported that approximately 45,000 new cases of MDS were diagnosed in individuals aged 65 years in the United States in 2003.⁵ This was likely an overestimation because the *International Classification of Diseases*, Ninth Revision (ICD-9) code used in this study to ascertain patients with MDS from Medicare claims was not specific to MDS, and included other hematopoietic conditions.⁶ Another recent publication based on the SEER–Medicare database suggests that the incidence of MDS is as high as 75 per 100,000 persons aged 65 years.⁷

Exactly how many incident cases of MDS occur in the United States is not completely resolved. Population-based cancer registries, such as the SEER Program are usually the authoritative source of information for cancer morbidity and mortality in the country. As with the surveillance of many other diseases, the completeness of case ascertainment was a concern shortly after MDS became a reportable condition. As observed with the SEER Program data, the age-adjusted incidence rate of MDS was 3.6 cases per 100,000 persons per year in the first year that MDS was reportable (2001), had increased to 3.8 cases per 100,000 persons per year in the following year (2002), and ranged from 4.1 to 4.6 cases per 100,000 persons per year during 2003 to 2008.⁸ This suggests that MDS case ascertainment might have been incomplete in the first 2 years of reporting, but has improved and become stable over time. A diagnosis of MDS can be made in the outpatient setting with bone marrow specimens reviewed by pathology laboratories, without visiting a hospital. If a cancer registry has incomplete coverage of pathology laboratories, a diagnosis of MDS may be missed. There are regional variations in the incidence rate of MDS,⁸ some of which may be attributable to the varying patterns of case ascertainment.

Existing data consistently suggest that MDS is predominantly a disease of the elderly (Figure).⁸ Approximately 86% of patients with MDS were aged 60 years at the time of their diagnosis (median age, 76 years), and only 6% of cases were diagnosed in those aged 50 years.³ Men have a higher incidence rate than women, and white individuals have a higher incidence rate than other racial/ethnic groups.³ With an aging population, an increasing rate of secondary MDS, improved awareness of the disease, and more thorough clinical workups, it is likely that the number of new patients diagnosed with MDS each year will increase in the future. Indeed, emerging evidence suggests that MDS is more common than previously believed.

Prevalence reflects the percentage of a population that lives with a disease. Clinically, prevalence is sometimes used interchangeably with the total number of patients who live with a disease, but strictly speaking prevalence is a percentage. Estimates of the number of people living with MDS are elusive. Preliminary data from Germany reveal an MDS prevalence of 20.7 cases per 100,000 people. Applying a similar prevalence to the population of the United States would result in an estimated 60,000 patients with MDS.⁹ In the noninstitutionalized United States population assessed in the 1988 to 1994 third National Health and Nutrition Examination Survey (NHANES III), 11.0% of men and 10.2% of women aged 65 years had anemia and a third of those individuals were considered to have unexplained anemia.¹⁰ As 17.2% of patients with unexplained anemia have disease characteristics consistent with a diagnosis of MDS (i.e., macrocytosis, neutropenia, thrombocytopenia), MDS may actually be the underlying disease in some of these patients.¹⁰ This suggests that MDS may not be as rare a disease in the United States as

previously thought. As the cancer registry–based incidence of MDS is similar to that of AML and the survival rate of patients with MDS is considerably longer than compared with patients with AML, the prevalence of MDS is far greater than that of AML. Although the knowledge of MDS is increasing since it became reportable in SEER in 2001, compared with AML and many other types of hematologic malignancies MDS remains understudied and underserved from an epidemiologic perspective.^{3,4,9,11}

ETIOLOGY

Congenital diseases, such as Fanconi anemia, are known to increase the risk of MDS.¹² In addition, ionizing radiation and chemotherapy for a previous malignancy, and occupational exposure to benzene are also established risk factors.¹³ Patients with MDS who have a history of cancer treatment are considered to have “secondary” or “therapy-related” MDS, and they tend to have a much poorer prognosis. The WHO recommends that these cases be grouped with AML rather than with “Other” MDS.¹⁴ The most important source of benzene exposure in the general population is cigarette smoking.¹⁵ Currently, environmental risk factors linked to MDS include cigarette smoking,^{16–18} and exposure to solvents (through occupational exposure or hobbies such as painting)^{18,20} and pesticides^{18,20}; however, the findings are far from consistent. The relation between alcohol consumption and MDS has been assessed in several studies with conflicting results. Although alcohol consumption did not appear to affect the risk of MDS in some studies,^{21–23} Ido and colleagues reported a significant association between alcohol use and MDS (odds ratio, 2.15; 95% confidence interval [CI], 1.12 to 4.16) as well as a dose-response relation.²⁴ In contrast, a recent case-control study by Strom and associates found that the moderate consumption of wine was associated with a significantly decreased risk of MDS.¹⁸

Our research group was the first to report a significant association between body mass index (BMI) and the subsequent development of MDS.²³ Compared with individuals with a BMI score <25.0 (i.e., normal weight), the relative risks for those with a BMI score of 25.0 to 29.9 (i.e., overweight) and 30.0 (i.e., obese) were 1.15 (95% CI, 0.81 to 1.64) and 2.18 (95% CI, 1.51 to 3.17), respectively. This association was not affected by physical activity, smoking status, or alcohol intake, and there appeared to be a trend.²³ The findings were derived from a prospective cohort study with more than a half million participants, which was the first and only cohort study to evaluate MDS etiology.²³ We also found spatial and temporal clustering in the incidence of MDS²⁵; however, the cause for such clustering remains unknown.

PROGNOSTIC FACTORS

Our analysis of SEER Program data on MDS from 2001 through 2008 suggests that the observed 3-year survival rate is 42% and the 5-year survival rate is 29%.⁸ Previous studies have identified several prognostic factors, including age, sex, transfusion dependence, MDS subtype, bone marrow blast percentage, number of cytopenias, and cytogenetics.^{26,27} The latter 3 disease features represent major factors determining outcomes for patients with MDS in prognostic models such as the International Prognostic Scoring System (IPSS).²⁷ In addition to karyotype and MDS subtype, transfusion dependence is a key factor in the WHO-based Prognostic Scoring System (WPSS).²⁸ More recently, in a sample of >2,000 patients aged 65 years who were diagnosed with MDS in 2001 and 2002, we identified comorbidities²⁹ and socioeconomic status³⁰ as significant and independent predictors of MDS survival. In terms of comorbidities, different diseases or conditions appeared to have a varying impact on the prognosis of MDS. For example, congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) were associated with shortened survival, whereas diabetes and cerebrovascular diseases did not alter the prognosis of patients with

MDS.²⁹ These findings were not surprising because CHF and COPD can be severely exacerbated by anemia and infection, both hallmarks of MDS. Also, if a patient with MDS undergoes disease transformation to AML the presence of CHF can limit the potential for administration of anthracyclines, which are among the primary chemotherapeutic agents for leukemia, because of their cardiac toxicity. Given that a “typical” elderly oncology patient has 3 comorbid conditions,³¹ it is necessary to assess the relevance to MDS prognosis of different common conditions as well as the potential interaction between different conditions. Furthermore, it may be important for clinicians to incorporate comorbidities into the risk stratification of patients with MDS when evaluating treatment options.

SUMMARY

The MDS are a group of understudied hematologic disorders, and MDS may be the underlying condition affecting some elderly patients with unexplained anemia. Thus, the classification of MDS as a malignancy, the addition of MDS to cancer reporting, and the approval of new drugs for the treatment of MDS, are all welcome developments in MDS research. With the current demographic trend, increasing disease morbidity (both incidence and prevalence) is expected in the near future. More research is required to elucidate the etiology of MDS and to assess the role of a comprehensive list of factors in the prognosis of MDS. The ultimate goal is the development of preventive measures to reduce disease occurrence and to treat patients more effectively in order to reduce mortality and improve quality of life.

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Figure.

Incidence rate of myelodysplastic syndromes (MDS) in different age groups in the United States (2001 to 2008). (Adapted from NCI SEER*Stat Database.⁸)