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Review article

Management of older adults with myelodysplastic syndromes (MDS)☆

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ABSTRACT

The myelodysplastic syndromes (MDS) are a varied group of hematologic neoplasms that lead to bone marrow failure, and also carry a risk of progression to acute myeloid leukemia. Patients with MDS suffer significant impairments to both their quality of life and survival. Age is the dominant risk factor for the development of MDS, with a median age at diagnosis over 70 years. Consequently, patients with MDS frequently have concurrent comorbidities and/or frailty which may be coincident or related to the disease itself. Disease characteristics, degree of comorbidity, and presence of frailty all impact prognosis. Treatment of MDS focuses on supportive care, with disease-modifying approaches (chemotherapy and allogeneic hematopoietic cell transplantation) reserved for fit patients with high-risk disease. Care of patients with MDS requires understanding the disease in the context of an older population, and tailoring approaches to both disease risk and patient suitability for therapy.

Contents

1. The Myelodysplastic Syndromes (MDS)

The myelodysplastic syndromes (MDS) are a group of chronic myeloid-lineage hematologic neoplasms defined by progressive bone marrow failure [1,2]. Primarily affecting older patients, MDS is a stem cell disorder characterized by ineffective clonal hematopoiesis that results clinically in one or more peripheral blood cytopenias, the hallmark of the disease. At diagnosis, most patients have morphologically dysplastic bone marrows and an identifiable clonal, genetic lesion detectable either by conventional chromosome analysis and/or by assessment for gene-level mutations via molecular techniques [2–4]. Some patients also have excess marrow myeloblasts, which indicates more advanced disease. MDS is a genetically unstable condition with a risk of progression. This can take the form of either further marrow failure (accumulation in depth and number of cytopenias) or evolution to acute myeloid leukemia (AML), defined by the presence of 20% or more myeloblasts in the bone marrow or blood. Some patients with MDS are asymptomatic, while others experience a substantial symptom burden related to one or more of the prevalent cytopenias and/or the

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disease itself [1]. Survival of patients with MDS is varied, ranging from months to many years [5]. Here we review the epidemiology of MDS, factors that influence disease prognosis, and treatment approaches.

1.1. MDS is a Disease of Older Persons: Epidemiology and Biology

MDS is a disease of older persons [6]. The Surveillance, Epidemiology, and End Results (SEER) Program first began collecting information on MDS in 2001, and the first three years of data (2001–2003) were described in 2007 by Ma et al. [7] A median age of 76 years at MDS diagnosis was reported with almost all cases (86%) occurring in individuals 60 years and older. Over half (56%) of cases were in people 75 years or older. The epidemiology of MDS is reflective of the disease biology, which is likely a consequence of the aging process. Indeed, age is the primary risk factor for developing MDS with a notable lack of association between the syndromes and common cancer-causing exposures such as alcohol (which may actually be protective) [8] and diet, although a modest association with smoking has been reported [9,10]. As humans age, hematopoietic stem cells tend to accumulate mutations in DNA. When the acquisition of a mutation confers a growth advantage to a hematopoietic cell lineage, clonal hematopoiesis results. Clonal hematopoiesis is now recognized to be common in older adults without cancer, present in approximately 10% of individuals over age 70 [11,12]. While clonal hematopoiesis alone does not constitute disease, patients with clonal hematopoiesis are at risk for acquiring additional mutations that may lead to progression to MDS (or another hematologic disorder). Other known risk factors for MDS including exposure to prior chemotherapy, ionizing radiation, or environmental toxins. These are believed to create a predisposition to MDS via damage to the hematopoietic stem cell compartment [13]. Myelodysplasia in children and young adults is rare, and often the result of genetic predisposition or inherited bone marrow failure syndromes.

How big of a problem is MDS? Ma et al. initially reported approximately 10,000 incident cases of MDS per year in the United States (US); [7] however, it is now recognized that MDS is underreported to cancer registries such as SEER [14–16]. Cogle et al. [15] constructed a claims-based algorithm to assess MDS incidence in the SEER-Medicare population and estimated an incidence of 75 cases per 100,000 persons over age 65 compared to 20 cases per 100,000 previously reported by SEER alone, suggesting the annual incidence in older adults is perhaps 3 times higher. A report from the Dusseldorf MDS-registry reported incidence rates of MDS similar to the SEER data; in their region, 5 to 10 cases per 100,000 person-years were reported in those aged 60–69 and 15–20 cases per 100,000 person-years were reported in those aged 70–79 [17]. As it is common for cytopenias in olderpersons to be incompletely evaluated in clinical practice, the true prevalence of MDS may be far higher than any of these estimations suggest.

1.2. Predicting Disease Risk in MDS: Disease Characteristics, Comorbidity, and Frailty

Prognosis and treatment decisions in MDS are guided by a patient's estimated disease risk. Several risk scores have been developed to predict the natural history of the disease—specifically, length of survival and risk of progression to AML—in the absence of intervention. These risk scores integrate disease features at diagnosis including cytopenias, presence of excess bone marrow myeloblasts, and type of cytogenetic abnormalities [5,18]. The most commonly used scoring system is the International Prognostic Scoring System (IPSS) [5]. Published in 1997 by Greenberg et al., it has been in use for 2 decades. The IPSS divides patients into four risk categories (low, intermediate-1, intermediate-2, and high) with median survival ranging from 5.7 years (lowest risk group) to 0.4 years (highest risk group). The revised IPSS (IPSS-R) [18], published by the same authors in 2012, separates patients into five risk categories (very low, low, intermediate, high, and very high) by incorporating refined cytogenetic risk categories, accounting for depth rather than mere number of cytopenias, and assigning more weight to the degree of excess blasts. Median survival in the IPSS-R risk stratification scheme ranges from 8.8 years (lowest risk category) to 0.8 years (highest risk categories). There is also an age-adjusted version of the IPSS-R that accounts for age (IPSS-RA) [18].

Other scoring systems such as the MD Anderson risk model [19] and the WHO prognostic scoring system (WPSS) [20,21] similarly incorporate information about cytopenias, excess blasts, and cytogenetic features of the disease, and also include a varied number of other prognostic factors including performance status, age, transfusion dependence, and Word Health Organization (WHO) pathologic classification. Evidence of molecular gene level alterations are also sought at MDS diagnosis and are becoming increasingly relevant not only for confirming the diagnosis of MDS and understanding disease biology [3,4,22], but also for refining prognostic models [23]. Efforts are underway to more fully integrate clinical, pathologic, and genetic factors to predict survival in MDS.

Given the older age of the MDS population, it is critical that the impact of comorbidity and frailty also be considered [24]. In a patient cohort with a median age well above 70 years, it is not surprising that patients with MDS frequently have one or medical comorbidities [25,26]. Interestingly, an analysis by Goldberg et al. showed that patients with MDS had more comorbidities including cardiac events (73.2% vs 54.5%, $P < .01$), dyspnea (49.4 vs 28.5, $P < .01$), diabetes (40.0% vs 33.1%, $P < .01$), and sepsis (22.5% vs 6.1%, $P < .01$) than an age-matched Medicare population, suggesting that MDS directly and/or indirectly promotes the development of separate medical conditions [14]. The connection between MDS and some comorbid conditions—such as cardiovascular events due to anemia, or infections due to neutropenia—is logical. However, the association between MDS and increased rates of other diagnoses, such as diabetes, could also be related to increased contact with medical providers and opportunity for disease detection and evaluation. Of note, interesting work is currently underway to further define the connection between clonal hematopoiesis and cardiovascular disease. In a recent case control analysis, Jaiswal et al. [27] showed that clonal hematopoiesis was associated with coronary heart disease and early myocardial infarction. Seeking a biologic explanation for this phenomenon, Jasiwal et al. [27] as well as Fuster et al. [28] were able to demonstrate that clonal *TET2* mutations are associated with aberrant macrophage function which leads to accelerated atherosclerosis in mouse models [28]. It is likely that the link between *TET2* mutations and atherosclerosis is merely a single elucidated example of a broader influence of clonal hematopoiesis on human physiology.

Beyond recognizing the burden of medical comorbidity in MDS patients and exploring possible pathophysiologic connections, the impact of comorbidity on MDS prognosis is of practical importance to the treating oncologist. Several groups have recently undertaken studies to define the impact of comorbidity on prognosis in MDS patients and collectively generated a body of work [29–34]demonstrating that increased comorbidity negatively impacts survival (even accounting for traditional MDS risk factors) and that integration of comorbidity assessment to traditional risk stratification can improve prognostic accuracy. The hematopoietic stem cell transplantation comorbidity index (HCT-CI), developed for predicting transplant outcomes [35], has been shown to provide prognostic information for MDS patients not undergoing transplant [36,37]. Della Porta et al. subsequently developed a myelodysplastic syndrome-specific comorbidity index (MDS-CI) specifically to predict the effect of comorbidity on survival of patients with MDS [29]. They demonstrated that the MDS-CI improved risk stratification of patients already stratified by the WPSS disease risk index. We suggest that the MDS-CI be calculated in all newly-diagnosed patients with MDS, and that the HCT-CI additionally be calculated in all patients with high-risk disease being considered for allogeneic stem cell transplantation. These assessments provide additional information to help guide discussions about therapeutic options.

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