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Primary Myelodysplastic Syndromes: The Mayo Clinic Experience With 1000 Patients

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Abstract

Objectives: To share our 25 years of experience with patients with primary myelodysplastic syndromes (MDS) and to describe the natural history of the disease including presenting clinical and laboratory characteristics and long-term disease outcomes.

Patients and Methods: One thousand consecutive patients with primary MDS evaluated at Mayo Clinic between January 1, 1989, and May 1, 2014, were considered. The Revised International Prognostic Scoring System and other risk models were applied for risk stratification. Separate analyses were conducted for patients diagnosed before 2005 (n=531) and after 2005 (n=469).

Results: Eighty-five percent of patients were older than 60 years (median age, 72 years), with 69% being men. The median follow-up period was 27 months (range, 0-300 months), during which time 808 (81%) deaths and 129 (13%) leukemic transformations were documented. Median survival and leukemic transformation rates were similar in patients diagnosed before or after 2005, despite the significantly higher use of hypomethylating agents in the latter group: 33 months vs 28 months (P=.46) and 13% vs 10% (P=.92), respectively. Revised International Prognostic Scoring System risk distribution was similar in patients diagnosed before or after 2005 (P=.23): 17% were categorized as very low, 36% low, 21% intermediate, 15% high, and 11% very high risk, with a median survival of 72, 43, 24, 18, and 7 months, respectively (P<.001). We found Revised International Prognostic Scoring System cytogenetic risk categorization to be suboptimal in its performance, whereas contemporary prognostic models were broadly similar in their performance.

Conclusion: The poor outcome in patients with MDS does not appear to have improved over time. Current risk stratification systems for MDS are not substantially different from each other. There is a dire need for drugs that are truly disease modifying and risk models that incorporate prognostically relevant mutations.

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Myelodysplastic syndromes (MDS) are malignant hematopoietic stem cell disorders categorized under chronic myeloid malignancies according to the World Health Organization (WHO) 2008 classification.[1,2] Myelodysplastic syndromes may be further subcategorized as primary (de novo) or secondary arising from previous chemotherapy, radiation therapy, or antecedent myeloid malignancies. Myelodysplastic syndromes may include a heterogeneous group of disorders that are characterized by dysplastic and ineffective blood cell production leading to peripheral blood cytopenias despite a hypercellular bone marrow, likely as a result of increased apoptosis in the marrow.[3] The pathophysiology of the disease remains largely elusive. The only exception is MDS with del(5q), in which haploinsufficiency of the ribosomal gene *RPS14* (for expansion of gene symbols, see www.genenames.org), which is required for the maturation of 40S ribosomal subunits and maps to the commonly deleted region, and homozygous inactivation of the casein kinase 1A1 gene (*CSNK1A1*) play a central role in disease

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biology.[4,5] Subsequently, in recent years, the discovery of several recurrent genetic abnormalities involving signal transduction (*NRAS*, *KRAS*, and *CBL*),[6] transcription regulation (*RUNX1*),[7] epigenetic regulation (*ASXL1*, *DNMT3A*, *TET2*, *EZH2*, and *IDH1/2*),[8-12] spliceosome machinery (*SF3B1*, *SRSF2*, *U2AF*, and *ZRSR2*),[13] and DNA repair (*TP53*)[14] have provided insight into the clinical heterogeneity of these disorders. For instance, mutations in the spliceosome component *SF3B1* correlate with the presence of ringed sideroblasts.[15] Of note, mutations involving these genes are not specific to MDS and occur at a variable frequency in other myeloid malignancies.[16]

Most patients with MDS are elderly, with a median age of 70 years, and typically present with complications associated with peripheral blood cytopenias. The clinical heterogeneity of MDS with an extremely variable risk of disease transformation to acute myeloid leukemia explains the variation observed in survival, ranging from only a few months to almost a decade. Hence, treatment options vary from watchful waiting and supportive care to disease-modifying therapy and allogeneic bone marrow transplant. The latter is the only potentially curative treatment option that is limited to patients younger than 70 years and comes with a potential cost of significant treatment-related morbidity and mortality.[17] Given the variable clinical course, an accurate prognostic assessment becomes critical. To that end, over the years, several prognostic scoring systems have been developed, starting with the International Prognostic Scoring System (IPSS) in 1997.[18] This was followed by the World Health Organization Prognostic Scoring System (WPSS) in 2007,[19] the global MD Anderson score (MDAS) in 2008,[20] and the most recent Revised International Prognostic Scoring System (IPSS-R) in 2012.[21] Each of these scoring systems uses readily available clinical and morphological variables, such as marrow blast percentage (IPSS, IPSS-R, and MDAS), karyotype (IPSS, IPSS-R, WPSS, and MDAS), number (IPSS) or degree of cytopenias (IPSS-R and MDAS), age (MDAS), WHO morphological classification (WPSS), transfusion dependence (WPSS and MDAS), and performance status (MDAS). With the advent of genome sequencing and identification of recurrent mutations of prognostic relevance, it is reasonable to expect the incorporation of molecular variables in future prognostic scoring systems.[22,23]

In the present study, we share our decades worth of experience with 1000 consecutive patients with primary MDS evaluated at Mayo Clinic with the following main objectives: (1) to provide a comprehensive description of clinical, laboratory, and morphological characteristics at diagnosis and (2) to validate prognostic factors predictive of survival and evolution to acute leukemia followed by (3) the application of currently available prognostic scoring systems and (4) comparison of clinical characteristics and survival of patients diagnosed before and after 2005.

PATIENTS AND METHODS

After approval by the institutional review board, we retrospectively recruited 1000 consecutive patients with primary MDS who were untreated at the time of referral to Mayo Clinic in Rochester, Minnesota, during the time period January 1989 to May 2014. A thorough review of medical records was conducted to ensure the inclusion of patients with primary MDS only. The diagnosis of MDS and leukemic transformation (LT) was made according to the WHO criteria.[1] The following MDS morphological categories were considered: refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia (RCMD), RCMD with ringed sideroblasts, refractory anemia with excess blasts-1 (RAEB-1), refractory anemia with excess blasts-2, MDS with isolated del(5q), and MDS unclassified. Patients with LT (>20% myeloblasts) at the time of evaluation and those with chronic myelomonocytic leukemia were excluded from the study. All morphological and cytogenetic assessments had to be either performed or reviewed at our institution for study inclusion. The bone marrow slides were not rereviewed for the purpose of this study. Classification and any pertinent morphology findings were based on the original bone marrow pathology report. Cytogenetic results were interpreted and reported according to the International System for Human Cytogenetic Nomenclature.[24] The definition of red cell transfusion dependency included patients presenting with symptomatic anemia that necessitated red cell transfusion and those with a history of red cell transfusions. However, only those patients with an ongoing need for red cell transfusions