Original Article

# Epidemiology, Natural History, and Practice Patterns of Patients with Myelodysplastic Syndromes in 2010

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**Key Words**

Myelodysplastic syndromes, epidemiology, risk factors, incidence, characteristics

**Abstract**

The incidence rate of the myelodysplastic syndromes (MDS) in the United States is approximately 3.4 per 100,000 people, accounting for more than 10,000 new diagnoses annually and an estimated 60,000 people living with the disease. Common risk factors for developing MDS include advanced age, male gender, and antecedent exposure to chemotherapy or radiation as treatment for other cancers, which alone accounts for 10% of MDS cases. Patients with MDS typically are diagnosed when they are in their 70s, have significant cytopenias, and have substantive transfusion needs. Erythropoiesis stimulating agents are used by more than 50% of patients, although the use of disease-modifying agents is increasing, and may ultimately have an impact on the number of patients living with MDS. (*JNCCN* 2011;9:57–63)

The first description of patients with a blood picture compatible with the myelodysplastic syndromes (MDS) was published at the beginning of the 20th century,[1] and the first MDS case series was published in the early 1970s.[2] This places the recognition of MDS up to 100 years behind what has occurred for other hematologic malignancies. Elucidation of the epidemiology, natural history, and practice patterns has similarly lagged behind that of other cancers.

However, the availability within the past decade of 3 drugs, azacitidine, lenalidomide, and decitabine,[3–5] which were approved by the FDA specifically for the treatment of MDS, has partly spurred the maturation rate of epidemiologic knowledge. This has also caused more attention to be focused on the evolution of lower- and higher-risk MDS into more aggressive forms of either MDS or acute myeloid leukemia (AML), and has necessitated a clearer description of how these drugs are being used across the country.

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## MDS Epidemiology

### Incidence and Prevalence

In 2001, the SEER program of the NCI and CDC began to track incidence rates of MDS. Based on the data collected from 2001 to 2003, the age-adjusted incidence rate of MDS in the United States was estimated to be 3.4 per 100,000 people, which translates to approximately 10,000 new cases per year.[6] Not surprisingly, the incidence rate increased over these 3 years, from 3.3 per 100,000 people in 2001, to 3.4 in 2002, and then to 3.6 in 2003, largely because of improved reporting practices within cancer registries.[7] In 2004, the incidence rate was estimated at 3.8 per 100,000 people, which is higher than that for AML, potentially making MDS the most common type of myeloid malignancy, with new yearly diagnoses estimated to be closer to 15,000. As one would expect of a disease primarily affecting older adults, incidence rates were lowest for people younger than 40 years, at 0.14 per 100,000, and highest with increasing age, reaching a level of 36 per 100,000 for patients aged 80 years and older. One recent study reported the 2003 incidence rate among U.S. Medicare

beneficiaries was as high as 162 per 100,000, although this is believed to be a vast overestimate related to inaccuracies in diagnoses.[8] This highlights the challenge in accurately determining the incidence rate; because the diagnostic criteria are at least somewhat subjective, incidence may be underestimated (if the diagnosis is missed by an inexperienced pathologist) or overestimated (if MDS is identified based on minimal dysplastic changes). The incidence rate in the United States is similar to that reported in western European countries, such as England/Wales and Sweden (3.6/100,000), Germany (4.1/100,000), and France (3.2/100,000), but higher than in Japan (1.0/100,000).[9–12]

Accurate prevalence statistics for MDS are difficult to identify in terms of the numbers of people living with the disease as opposed to new diagnoses. Preliminary data from Germany show a prevalence rate of 12.4 per 100,000 people.[13] If incidence, and thus prevalence rates, between the United States and Germany are assumed to be similar, this would translate to approximately 60,000 people living with MDS in the United States. However, even this is believed to be an underestimate. Guralnik et al.[14] reported an overall prevalence of anemia of 10.6% in the United States in 2004, based on 2000 blood samples collected from people aged 65 years or older as part of the third National Health and Nutrition Examination Survey. Within the category of "unexplained anemia," 17% of people had a macrocytic anemia, leucopenia, or thrombocytopenia, which are peripheral blood findings typical of MDS. This would translate to 170,000 people living with MDS in the United States, again highlighting the diagnostic challenge of the disease. Importantly, however, these data were generated before the approval of MDS therapies by the FDA. Because at least one of these therapies (azacitidine) has shown a survival advantage in higher-risk patients with MDS,[15] prevalence rates can be expected to increase as patients are living longer with their disease and MDS awareness is becoming heightened among primary care physicians. Thus, although a prevalence of 170,000 people with MDS can be assumed to be an overestimate, a rate of 60,000 people likely underestimates the impact of the disease.

## Risk Factors for Developing MDS

The greatest risk factor for developing MDS is advanced age, with yearly incidence rates increasing 10-fold for octogenarians compared with the rest of the population. Men also have an increased incidence rate compared with women (4.4 vs. 2.2 per 100,000), as do whites compared with blacks (3.3 vs. 2.4 per 100,000; Table 1).

Secondary MDS accounts for approximately 10% of all MDS diagnoses. Most cases arise after chemotherapy for other cancers, with alkylating agents and topoisomerase inhibitors the most well-described, and after radiation therapy.[9,16] The typical latency period for secondary MDS after exposure to alkylating agents or radiation therapy is 5 to 7 years. The risk seems to be dose-dependent,[17,18] and is associated with unbalanced translocations involving chromosome 5 or 7, or complex cytogenetics.[19] MDS after exposure to topoisomerase inhibitors is less common, with a latency period of approximately 2 years,[20] and is associated with a balanced translocation involving 11q23 (the *MLL* gene). Long-term prognosis is poor for either type of secondary MDS.[21,22] As other malignancies become more successfully treated with chemotherapy and radiation therapy, the rate of secondary MDS is anticipated to increase.

Two major studies have explored the rates of secondary MDS and AML among patients with non-Hodgkin's lymphoma who have undergone autologous bone marrow transplantation.[23,24] In both series, rates of secondary MDS/AML approached 7% at 10 years, or 20% at 20 years of follow-up. All of these patients were heavily pretreated with alkylating agents and topoisomerase inhibitors, and received cyclophosphamide/total body irradiation or busulfan/cyclophosphamide preparative regimens for their transplantation. Case reports/series also describe MDS development after use of these agents to treat other cancers, such as breast, and after use of purine analogs for lymphoid malignancies.[18,25–36] MDS may also evolve from an antecedent hematologic disorder, particularly polycythemia vera, after treatment with alkylating agents or p32.[37]

A recent meta-analysis of 10 studies, comprising 2105 cases and 3363 controls, examined the association between smoking and the development of MDS.[38] The odds ratio for MDS developing in smokers was 1.45 (95% CI, 1.21, 1.74), indicating a 45% increase in risk. The association between alcohol intake and MDS was 1.31 (95% CI, 0.79–2.18), indicating a possible 31% increased risk, although CIs crossed parity.

**Table 1 Risk Factors for Developing Myelodysplastic Syndromes**

| Risk Factor | Relative Impact |
|---|---|
| Advanced age | + + + + + |
| Exposure to chemotherapy or radiation therapy for another cancer | + + + + |
| Male gender | + + + |
| White race | + + + |
| Occupational/environmental exposure to organic solvents | + + + |
| Smoking | + + |
| Agricultural chemicals, pesticides, other solvents | + |

MDS can arise after environmental and occupational exposure to organic solvents, such as benzene and its derivatives. This has been well described in patients working in the rubber and oil industries.[39,40] Case-control studies confirm an increased risk of MDS from exposure to agricultural chemicals (insecticides, pesticides, herbicides or fertilizer, with an odds ratio of 4.6 [95% CI, 1.6–12.7]), solvents (odds ratio, 2.1; 95% CI, 1.2–2.5), and radiation.[41,42] Other studies have linked the development of MDS to exposure to genotoxic industrial agents, including radiation, halogenated organics, metals, and petroleum products, in addition to pesticides and solvents.[43,44]

## MDS Natural History

Clinically, the natural history can be predicted based on a patient's prognostic score, using the International Prognostic Scoring System (IPSS) or another system such as the World Health Organization Prognostic Scoring System or one developed by the MD Anderson Cancer Center, and the pathologic classification. As a general statement, patients with poor-risk cytogenetics (including complex cytogenetics and chromosome 7 abnormalities), excess (≥ 5%) myeloblasts, and multiple cytopenias, or who are dependent on red blood cell transfusions, have higher-risk MDS (patients with excess blasts using French-American-British [FAB] or WHO criteria, or IPSS scores of intermediate-2 or high) and a median survival of less than 2 years (patients with all 3 poor-risk clinical findings have a median survival < 6 months). However, those with good-risk cytogenetics (normal, del(5q), -Y, or del(20q)), a low (< 5%) blast percentage, and minimal cytopenias have lower-risk MDS (FAB categories of refractory anemia [RA] and RA with ring sideroblasts (RARS); WHO categories of RA, RARS, refractory cytopenia with multilineage dysplasia (RCMD), RCMD with ring sideroblasts, MDS with deletion of chromosome 5q (del(5q)), and MDS unclassified; and IPSS scores of low and intermediate-1 with a median survival of 3 to 8 years.[45–47]

A glimpse into the natural history of MDS in the United States can be derived from data reported by SEER and the North American Association of Cancer Registries (NAACR)[7]; from a recent study characterizing patients with MDS that was based on more than 4500 surveys completed by 101 physicians[16]; and from a survey of 358 MDS patients conducted over the Internet.[48]

Almost 25,000 patients representing 82% of the United States population contributed data to the SEER/NAACR study from 2001 to 2003.[7] Age-dependent incidence rates, racial differences, and male predominance were discussed earlier. The SEER/NAACR report was able to examine MDS subtypes, identifying 28.5% of patients with MDS as having lower-risk disease (defined as those with RA or RARS; refractory cytopenia with multilineage dysplasia; and MDS with del(5q)) and 13% of patients as having higher-risk disease (defined as those having excess blasts). However, and again reflecting the learning curve for cancer registries in identifying MDS diagnoses, 56% of patients were classified as "MDS not otherwise specified." The 3-year relative survival rates for all patients with MDS was 45%, and was lower for patients with chronic myelomonocytic leukemia, considered separately from MDS, at 21%.

In the physician survey study[16] of 4514 patients, 670 were newly diagnosed, 45% of whom were women; the remainder were established patients. The median age at diagnosis was 71 years, whereas among

established patients it was 72 to 75 years (Table 2). Secondary MDS was seen in approximately 10% of all patients after chemotherapy (76%), radiation (~ 15%), or chemical exposure (5%).

The typical patient with recently diagnosed MDS had some degree of pancytopenia, with a median hemoglobin value of 9.1 g/dL, median platelet count of 100,000/mm$^3$, and median neutrophil count of 1780/mm$^3$. Only a mean of 16% had 1% to 5% circulating blasts, whereas a mean of 10% had more than 5% blasts. Cytogenetics were available on approximately 90% of patients. Using IPSS cytogenetics risk groups, 51% of recently diagnosed patients were classified as good, 20% as intermediate, and 17% as poor, similar to percentages seen in the original IPSS publication and in German cytogenetics data. The most commonly reported abnormality was del(5q), which occurred in 11% of recently diagnosed patients.

Lower-risk MDS was more common than higher-risk MDS among both recently diagnosed cases (68%–69% vs. 31%–32%, respectively) and established cases (approximately 80% vs. 20%, respectively), depending on criteria used.

Patients with MDS had high transfusion requirements. Among patients with newly diagnosed lower-risk MDS, 22% required red blood cell transfusions, and 57% had previously received one. A smaller percentage of patients (5.5%), were dependent on platelet transfusions, whereas 37% had previously received a platelet transfusion. In patients with newly diagnosed higher-risk MDS, however, 68% were dependent on red blood cell transfusions, and 88% had previously received a transfusion. Furthermore, 33% were dependent on platelet transfusions, with 58% having received one at some point.

Results from the patient survey[48] support those from the physician survey, and provide some more

**Table 2 Survey-Based Characteristics of Patients With MDS**

| | | Physician Survey | Patient Survey* |
|---|---|---|---|
| Age (median) | Newly diagnosed | 71 y | |
| | Established | 72–75 y | 65 y |
| Sex (mean) | Male | | |
| | • Newly diagnosed | 55% | |
| | • Established | 51%–57% | 49% |
| Duration of MDS (median) | | 13–16 mo | 36 mo |
| MDS status | Primary | 88%–93% | N/A |
| | Secondary | 7%–12% | |
| Secondary cause | Chemotherapy | 55%–80% | |
| | Radiation | 6%–21% | |
| | Chemical exposure | 2%–9% | |
| Presenting blood counts (median) | Hemoglobin (g/dL) | 9.1 | 82% anemic |
| | Platelet (x 10$^3$/mm$^3$) | 100 | 46% thrombocytopenic |
| | Neutrophil (x 10$^3$/mm$^3$) | 1.78 | 45% neutropenic |
| IPSS risk group (6% missing) | Low | 30% | 28% |
| | Intermediate-1 | 34% | 39% |
| | Intermediate-2 | 16% | 23% |
| | High | 13% | 9% |

Abbreviations: IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; NA, not available.
*Does not distinguish newly diagnosed from established patients.
Data from Sekeres MA, Schoonen WM, Kantarjian H, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst 2008;100:1542–1551; and Smith RE, Bryant J, DeCillis A, Anderson S. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project Experience. J Clin Oncol 2003;21:1195–1204.

insight into the natural history of MDS. In 2009, 358 patients affiliated with the Aplastic Anemia & MDS International Foundation (AAMDS) responded to an e-mail survey to assess perceptions of disease state, prognosis, and treatment outcomes. The median age was 65 years and median duration of MDS was 3 years, with patients reporting first detection of abnormal blood counts a median of 3 years before their diagnosis. Similar to the physician survey, most respondents had lower-risk disease (68%) and had significant cytopenias: 82% had anemia, 46% thrombocytopenia, and 45% neutropenia. Furthermore, 65% previously received a blood transfusion, 52% of which had been given within the prior 3 months; 64% had been receiving blood transfusions for 1 year or longer; and 60% received transfusions once monthly or more frequently.

Among patients completing the survey, understanding of the disease was poor: 55% did not know their IPSS risk score or category, 45% did not know their blast percentage, and 28% did not know their cytogenetics status. Understanding of reasonable treatment goals also was poor: 37% of patients believed that their most recent or current treatment would increase their chances of survival; 26% felt their current therapy had a greater than 50% chance of improving their survival; and 36% were uncertain about how their treatment would affect their prognosis. Of all survey participants, 16% agreed that their most recent or current treatment could be curative (with 10% believing this to have a > 50% chance of being true), whereas 40% were uncertain.

Although both the physician and patient survey studies have limitations, because they both rely heavily on recall and responses could not be verified independently, results from the patient survey show that patients had not been informed of the natural history of their disease, including disease severity, regardless of the treatment they were receiving.

## MDS Practice Patterns

Although SEER and the NAACR do not capture information about how patients with MDS are treated, this information can be derived from the physician and patient survey results, which again support each other in their findings. The general recommendation is to treat patients with lower-risk MDS with watchful waiting, erythropoiesis stimulating agents (ESAs), or lenalidomide, whereas higher-risk patients, in whom these drugs have limited efficacy, should be treated with hypomethylating agents or hematopoietic stem cell transplantation.[49,50]

Regardless of timing of diagnosis or severity of MDS, ESAs were used by more than 50% of patients with MDS in both surveys. These surveys diverged in their reporting of the use of disease-modifying therapies, such as azacitidine, decitabine, and lenalidomide. In the physician survey, fewer than 10% of patients were reported to be receiving one of these drugs, whereas in the patient survey, respondents reported use of the drugs within the 3 months preceding the survey 39% to 56% of the time. The difference in drug use likely results from some degree of selection bias in the patient survey (because all patients were on mailing lists from AAMDS and thus had access to more information about MDS and its therapies, and were Internet savvy) and the difference in timing of the surveys, because the physician survey was conducted 2 to 4 years before the patient survey, when drug use was not as prevalent.

The only potentially curative therapy for MDS, bone marrow transplantation, had been performed or was being considered in fewer than 5% of all patients in the physician survey, and had been received by only 10% of subjects in the patient survey, even in the era of reduced-intensity conditioning transplantation. A similar low percentage of patients in the physician survey (< 5%) were enrolled in or being considered for a clinical trial, whereas in the patient survey, 24% reported having been on a clinical trial, again reflecting the difference in access to information and self-advocacy for patients affiliated with AAMDS.

## Conclusions

The epidemiology of MDS is evolving quickly as accuracy of reporting and physician understanding of the disease and treatment options progress. The societal impact of the disease, measured in numbers of people affected yearly with a new diagnosis or who are living with the disease, and in transfusion and therapeutic needs, is enormous. As disease-modifying agents truly start to change the natural history of MDS for the better, the prevalent population of MDS patients in the United States likely will increase. This, along with the aging of the population as a whole, will contribute to MDS becoming the most common myeloid malignancy.

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