Myelodysplastic Syndromes

Incidence and Survival in the United States

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Supported by a supplement to contract N01-PC-35133 between the National Cancer Institute's Surveillance, Epidemiology, and End Results Program and the Connecticut Department of Public Health and by a grant awarded by the National Cancer Institute (K07 CA119108).

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Received December 19, 2006; revision received December 23, 2006; accepted January 3, 2007.

BACKGROUND. Myelodysplastic syndromes (MDS) became reportable to the Surveillance, Epidemiology, and End Results (SEER) Program (the United States cancer surveillance program) in 2001. This provided the first opportunity to examine the incidence and survival of patients with MDS in the United States using a large, population-based database.

METHODS. The SEER 17 regions public-use database (November 2005 submission) was accessed to obtain data on the frequency, incidence, and survival of patients with MDS. Geographic areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high-quality, population-based cancer reporting system and for their epidemiologically significant population subgroups.

RESULTS. SEER data from 2001 through 2003 indicated that the risk of MDS increased with age, and approximately 86% of MDS cases were diagnosed in individuals aged $\geq$60 years (median age at diagnosis = 76 years). Men had a significantly higher incidence rate than women (4.5 vs 2.7 per 100,000 per year). Among racial groups, white individuals had the highest incidence rate. In 2003, approximately 10,300 incident cases of MDS were diagnosed in the United States. The survival of MDS patients was poor, with an observed 3-year survival rate of only 35% (5-year survival data were not available at the time of the current report). Male patients and patients who were diagnosed at an older age had significantly worse survival. MDS survival also varied by clinical subtype, and the survival of patients who had refractory anemia was somewhat worse than reported previously. The availability of descriptive epidemiologic data on MDS can be used now to facilitate much needed research on the etiology and outcome of MDS.

CONCLUSIONS. The current results indicated that >10,000 incident cases of MDS are diagnosed annually in the United States, and the survival of patients with MDS is poor. The availability of descriptive epidemiologic data on MDS can be used now to facilitate much needed research on the etiology and outcomes of MDS. ***Cancer* 2007;109:1536–42.** © *2007 American Cancer Society.*

KEYWORDS: myelodysplastic syndromes, incidence, survival, Surveillance, Epidemiology, and End Results Program.

The myelodysplastic syndromes (MDS), also known as myelodysplasia, are a group of chronic conditions that involve persistent peripheral blood cytopenias. Because of the lack of large, population-based studies, the incidence of MDS in the United States has not been well documented. Estimates from 1995 suggest that there were approximately 1500 new cases each year in the United States,[1] whereas a more recent estimate was as high as 15,000 new cases each year.[2] Population-based survival data in the United States also are lacking. In 2001, MDS became reportable to the Surveillance,

Epidemiology, and End Results (SEER) Program, which consists of high-quality, population-based cancer registries that are supported and sponsored by the National Cancer Institute.[3] The SEER Program is the authoritative source on cancer incidence and survival in the United States. The current analysis, which was based on SEER data from 2001 through 2003, is the first assessment to our knowledge of the incidence and survival of MDS using a large, population-based database in the United States. SEER data from more recent years were not available at the time of this report.

MATERIALS AND METHODS

Source of Data

The SEER 17 regions public-use database (November 2005 submission) was accessed to obtain data on the frequency, incidence, and survival of MDS.[4] Geographic areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high-quality, population-based cancer reporting system and for their epidemiologically significant population subgroups. The population covered by SEER is comparable to the general United States population with regard to measures of poverty and education. The SEER population tends to be somewhat more urban and has a higher proportion of foreign-born individuals than the general United States population.[5] The 17 SEER regions cover approximately 26.2% of the United States population and include the states of Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah; the metropolitan areas of Atlanta, Detroit, Los Angeles, San Francisco-Oakland, San Jose-Monterey, and Seattle (Puget Sound); as well as California (excluding San Francisco-Oakland, San Jose-Monterey, and Los Angeles), rural Georgia, and American Indians/Alaska Natives residing in the state of Alaska. In 2003, the most recent year for which SEER data are available, the total population in the 17 regions exceeded 76 million. All incident MDS cases (histology type International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes 9980, 9982–9987, and 9989) diagnosed from 2001 to 2003 that were reported to the SEER Program were included in this analysis.

MDS is heterogeneous both biologically and clinically. The development of diagnostic criteria was addressed first in 1974 and 1975 by a group of prominent hematologists known as the French-American-British (FAB) Cooperative Group.[6] The FAB classification of MDS includes 1) refractory anemia (RA), 2) RA with ringed sideroblasts (RARS), 3) RA with excess blasts (RAEB), 4) RAEB in transformation (RAEB-T), and 5) chronic myelomonocytic leukemia with white blood cell counts $\leq$12,000 μL.[7] The World Health Organization (WHO) published its recommendation for classification of MDS in 1999[8] and published a clarification and rationale for differences between the FAB and WHO classifications in 2002.[9] The WHO recommendation for the classification of MDS includes 1) RA, 2) RARS, 3) refractory cytopenia with multilineage dysplasia (RCMD), 4) RCMD and ringed sideroblasts (RCMD-RS), 5) RAEB-1, 6) RAEB-2, 7) MDS associated with isolated 5q deletion, and 8) MDS, unclassified.

The MDS histology types recorded in SEER are based onICD-O-3 codes, which are not 100% consistent with either the FAB classification or the WHO recommendation. The 8 ICD-O-3 codes that are included in SEER for MDS are 9980 (RA), 9982 (RARS), 9983 (RAEB, including RAEB under the FAB classification and both RAEB-1 and RAEB-2 under the WHO recommendation), 9984 (RAEB-T), 9985 (RCMD), 9986 (MDS associated with 5q deletion), 9987 (therapy-related MDS), and 9989 (MDS, not otherwise specified).

Data Analyses

The SEER*Stat program (version 6.2.4; National Cancer Institute) was used to 1) estimate incidence rates and corresponding confidence intervals, 2) calculate observed survival and relative survival, and 3) generate a list of MDS patients with information on other tumors recorded in SEER. The CanSurv program (version 1.0; National Cancer Institute) was used to fit semiparametric proportional hazard models to evaluate factors that influence survival. The SAS statistical software package (version 9.1.3 for Windows; SAS Institute) was used to assess the time interval between the diagnosis of previous primary tumors (when relevant; see below) and the diagnosis of MDS.

The incidence of MDS was described by age, sex, and race (white, African-American, American Indian/Alaska Native, and Asian/Pacific Islander). Included in the survival analysis was a subgroup of patients with MDS who fulfilled the following criteria: 1) diagnosed in 2001 or 2002, 2) actively followed by SEER for survival, 3) not identified from death certificates or autopsies only, and 4) did not have other primary tumors recorded in SEER prior to the diagnosis of MDS. The last criterion was applied because there was a concern that the survival of patients with MDS who had previous tumors may be affected by their other primary tumors or by the treatment they received for those tumors. Patients who were diagnosed in

2003 were excluded because they would not have had >12 months of follow-up by the end of 2003, when the survival data were censored. Because the November 2005 submission of SEER data only included survival information through December 2003, the survival of patients with MDS beyond 36 months could not be evaluated with the data available.

Observed survival was calculated using the actuarial method, also known as the life-table method, with 3-month intervals. For an individual patient, the expected survival is generated based on United States life tables matched to the individual on age, sex, race, and year of diagnosis, and the relative survival equals observed survival divided by expected survival. A relative survival <1 indicates that an individual has a poorer survival than the United States general population with the same age, sex, and race at the same calendar time. Survival measures were reported by age, sex, race, and major MDS subtypes, including RA (histology type ICD-O-3 code 9980), RARS (histology type ICD-O-3 code 9982), and RAEB (histology type ICD-O-3 code 9983). In addition, hazard ratios and their corresponding 95% confidence intervals (95% CIs) were estimated for demographic factors that were associated significantly with the relative survival of patients with MDS. The survival of other subtypes was not described separately because of the small number of patients reported to SEER.

Patients with MDS who had previous primary tumors were identified. The type of their previous tumors and the time intervals between the diagnosis of previous tumors and the diagnosis of MDS were assessed. Two different time intervals were calculated: 1) the interval between the diagnosis of the first primary tumor and the diagnosis of MDS and 2) the interval between the diagnosis of the most recent non-MDS primary tumor and the diagnosis of MDS.

RESULTS

The SEER 17 regions public-use database (November 2005 submission) included a total of 7131 MDS diagnoses during 2001 to 2003, of which 3828 (53.7%) were men, and 3303 (46.3%) were women. The majority of MDS cases were diagnosed in older individuals, and the median age at diagnosis was 76 years. The percentages of patients diagnosed in individuals aged ≥60 years, ≥65 years, ≥70 years, and ≥75 years were 86.4%, 80.0%, 70.3%, and 55.9%, respectively. For both men and women, the risk of MDS increased with age (Table 1).

TABLE 1
Age-Specific Incidence Rates of Myelodysplastic Syndromes in the United States, 2001–2003: The Surveillance, Epidemiology, and End Results Program 17 Regions Public-use Database, November 2005 Submission

	Men and women		Men		Women	
Age, y	Count	Rate*	Count	Rate*	Count	Rate*
0	8	0.2	3	0.2	5	0.3
1–4	26	0.2	13	0.2	13	0.2
5–9	10	0.1	2	0	8	0.1
10–14	12	0.1	5	0.1	7	0.1
15–19	17	0.1	8	0.1	9	0.1
20–24	12	0.1	9	0.1	3	0
25–29	18	0.1	11	0.1	7	0.1
30–34	30	0.2	22	0.3	8	0.1
35–39	58	0.3	33	0.4	25	0.3
40–44	100	0.6	56	0.6	44	0.5
45–49	148	0.9	72	0.9	76	0.9
50–54	216	1.5	112	1.6	104	1.4
55–59	314	2.8	161	2.9	153	2.6
60–64	460	5.4	257	6.3	203	4.6
65–69	686	10	386	12.2	300	8.1
70–74	1032	16.6	599	21.8	433	12.6
75–79	1374	25.7	785	35.7	589	18.7
80–84	1406	36.2	729	48.9	677	28.3
≥85	1204	36.4	565	54.7	639	28
Total	7131		3828		3303	

* Rates are per 100,000 per year.

Men had a significantly higher incidence rate than women. The age-adjusted incidence rate for MDS in men was 4.5 per 100,000 per year with a 95% confidence interval (95% CI) of 4.3 to 4.6 per 100,000 per year, whereas the rate for women was 2.7 per 100,000 per year (95% CI, 2.6–2.8 per 100,000 per year). Of all racial groups, whites had the highest incidence rate, whereas American-Indians/Alaska Natives and Asian/Pacific Islanders had lower rates (Table 2).

The incidence of MDS varied slightly by calendar year. The age-adjusted incidence rate was 3.28 per 100,000 per year (95% CI, 3.15–3.42 per 100,000 per year) in 2001, 3.37 per 100,000 per year (95% CI, 3.23–3.51 per 100,000 per year) in 2002, and 3.56 per 100,000 per year (95% CI, 3.42–3.70 per 100,000 per year) in 2003.

Applying the age-, sex-, and race-specific incidence rates of MDS in the SEER population for 2003 to the entire United States population (based on Census estimates) resulted in an estimated total of 10,301 incident MDS patients who were diagnosed in the United States in 2003. Applying the 2003 age-adjusted incidence rate of 3.56 to the entire United

States population generated an estimated total of 10,351 (95% CI, 9951–10,764) incident MDS patients.

Included in the survival analysis was a subgroup of 3389 MDS patients who were 1) diagnosed during 2001 and 2002, 2) followed actively by SEER for survival, 3) not identified from death certificates or autopsies only, and 4) had MDS as their first primary tumor. Observed and relative survival percentages are presented by demographic factors (Table 3). The 3-year observed survival for patients with MDS was 35%, and the 3-year relative survival rate was 42%. When age, sex, and race were included simultaneously in a multivariate proportional hazard model, age and sex were associated significantly with the relative survival of patients with MDS, whereas race did not appear to be an important determinant. Based on estimates from a model with both age and sex, men with MDS were 25% more likely to die than women (hazard ratio, 1.25; 95% CI, 1.14–1.36).

TABLE 2
Age-Adjusted Incidence Rates of Myelodysplastic Syndromes by Sex and Race in the United States, 2001–2003: The Surveillance, Epidemiology, and End Results Program 17 Regions Public-use Database, November 2005 Submission

	Rate (95% Confidence interval)*		
Variable	Men and women	Men	Women
All races	3.4 (3.3–3.5)	4.5 (4.3–4.6)	2.7 (2.6–2.8)
White	3.5 (3.4–3.6)	4.6 (4.5–4.8)	2.7 (2.6–2.8)
Black	3 (2.7–3.3)	3.5 (3–4)	2.7 (2.4–3.1)
American Indian/Alaska Native	1.3 (0.8–2.1)	1.8 (0.9–3.5)	1 (0.5–2)
Asian or Pacific Islander	2.6 (2.3–2.9)	3.2 (2.7–3.6)	2.2 (1.9–2.5)

95% CI indicates 95% confidence interval.
* All rates are per 100,000 per year and age-adjusted to the 2000 US standard population.

Compared with patients who were diagnosed at age <60 years, the mortality hazard ratios for those who were diagnosed at ages 60 to 69 years, 70 to 79 years, and ≥80 years were 1.21 (95% CI, 1.03–1.43), 1.33 (95% CI, 1.15–1.54), and 1.71 (95% CI, 1.47–1.98), respectively. The observed survival percentages of patients with MDS who were diagnosed at ages <50 years (n = 221 patients) and ≥50 years (n = 3168 patients) are presented in Figure 1. Again, patients with MDS who were younger at the time of diagnosis had better survival.

Of the patients with MDS who were included in the survival analysis, 1687 patients had no subtype specified, 563 patients had RA, 404 patients had RARS, 478 patients had RAEB, 67 patients had RAEB-T, 104 patients had RCMD, 64 patients had MDS with 5q deletion, and 22 patients had therapy-related MDS. The observed survival percentages of these groups are plotted in Figure 2. The observed survival for the period from 33 to 36 months after diagnosis is not presented, because no deaths occurred in patients with RARS or RAEB during that period, and the probability of surviving through that period could not be calculated. The median survival was 28 months for patients with RA and 11 months for patients with RAEB. Because >50% of patients with RARS survived for 3 years, the longest duration under observation, the median survival for patients with RARS could not be estimated with the current data, although it obviously exceeded 36 months.

Of the 7131 patients who were diagnosed with MDS during 2001 to 2003 and were reported to SEER registries, 998 patients (14%) had other primary tumors diagnosed prior to their diagnosis of MDS. Of 998 patients with MDS, 811 patients (81.3%) had

TABLE 3
Survival of Patients With Myelodysplastic Syndromes by Demographic Characteristics in the United States: The Surveillance, Epidemiology, and End Results Program 17 Regions Public-use Database, November 2005 Submission

	Cumulative observed survival (Cumulative relative survival), %								
		Age, y				Sex		Race*	
Months since diagnosis	Overall n = 3389	<60 n = 477	60–69 n = 563	70–79 n = 1187	≥80 n = 1162	Men n = 1828	Women n = 1561	White n = 2931	African American n = 257
6	79 (81)	89 (89)	82 (83)	81 (82)	72 (76)	78 (80)	81 (83)	79 (82)	78 (80)
12	66 (69)	76 (76)	70 (72)	67 (70)	58 (65)	63 (67)	69 (72)	66 (70)	68 (72)
18	54 (59)	66 (67)	61 (63)	56 (60)	44 (53)	51 (56)	58 (63)	54 (59)	59 (64)
24	47 (53)	60 (61)	54 (56)	50 (55)	37 (46)	45 (51)	50 (56)	47 (53)	54 (61)
30	41 (47)	54 (55)	50 (52)	42 (47)	31 (41)	38 (45)	45 (51)	41 (47)	46 (53)
36	35 (42)	47 (48)	—†	36 (42)	25 (35)	31 (37)	40 (47)	35 (43)	32 (38)

* Survival was calculated only for whites and African Americans because of the small numbers of patients in other racial groups.
† Survival could not be calculated because of the lack of deaths in the last 3-month interval (33–36 months postdiagnosis).

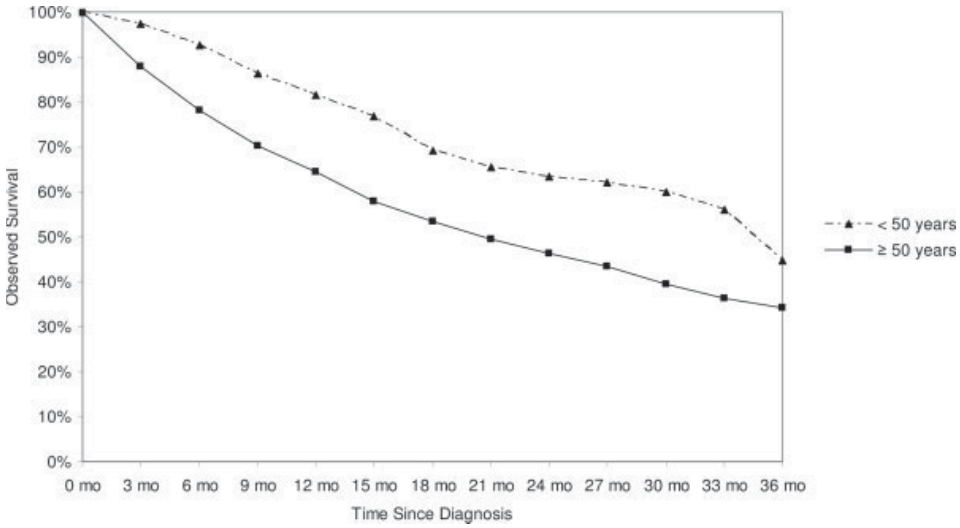

FIGURE 1. Observed survival of patients with myelodysplastic syndrome by age at diagnosis in the United States (Surveillance, Epidemiology, and End Results data, November 2005 submission[4]).

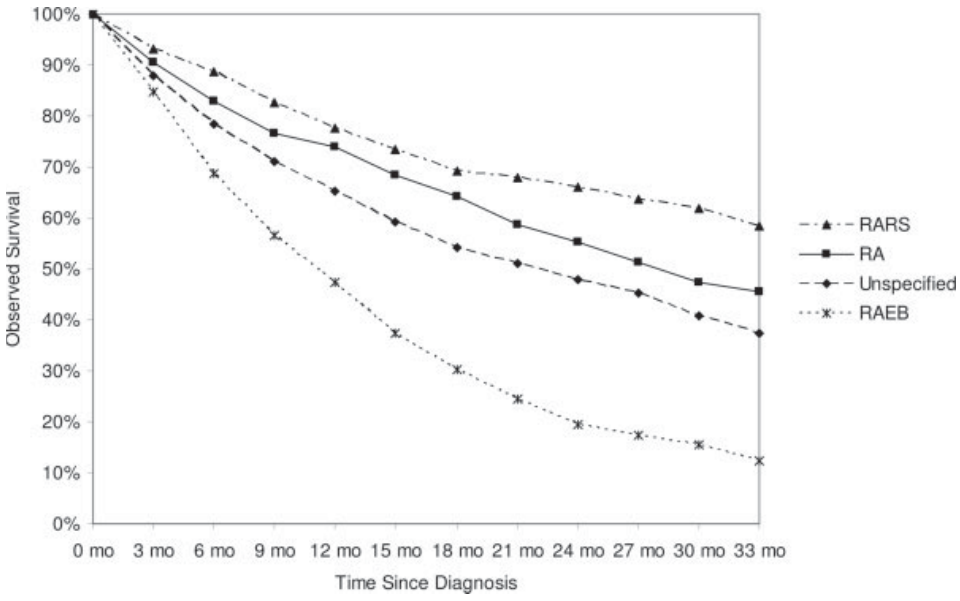

FIGURE 2. Observed survival of patients with myelodysplastic syndrome by subtype in the United States (Surveillance, Epidemiology, and End Results data, November 2005 submission[4]). RA indicates refractory anemia; RARS, RA with rare sideroblasts; RAEB, RA with excess blasts.

MDS as their second primary tumor, 161 patients (16.1%) had MDS as third primary tumor, and 26 patients (2.6%) had ≥3 other primary tumors prior to their diagnosis of MDS. The sites of the primary tumors varied, but the most common sites were prostate (19.9%), breast (16.5%), non-Hodgkin lymphoma (8.4%), urinary/bladder (6.0%), and lung and bronchus (5.6%). The median lag time between the diagnosis of the first primary tumor and MDS was 4.5 years (25th percentile = 1.6 years, 75th percentile = 9.4 years), and the median lag time between the diagnosis of the most recent non-MDS primary tumor and MDS was 3.8 years (25th percentile = 1.3 years, 75th percentile = 8.5 years).

DISCUSSION

To our knowledge, this analysis is the first to use large population-based data to evaluate the incidence and survival of MDS in the United States. The total population included in the SEER 17 regions ranged from 74 million to 76 million during 2001 to 2003; and, in total, 7131 MDS diagnoses were included in the analysis. We believe that the sample size is the largest ever, and the MDS incidence that we estimated from SEER data generally was consistent with what was reported previously in 2 other population-based studies that were conducted in Germany and the United Kingdom.[10,11] The German study estimated the incidence of MDS with approxi-

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