Chapter 1
Epidemiology, Etiology, and Clinical Presentation of Myelodysplastic Syndromes

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Introduction

Myelodysplastic syndromes (MDS) encompass a family of clonal myeloid stem cell disorders that increase with age, characterized by dysplastic and ineffective hematopoiesis and high frequency of cytogenetic abnormalities and genetic mutations. The disease frequently presents with peripheral blood cytopenias, macrocytosis, anisocytosis, and poikilocytosis and is diagnosed by bone marrow aspirate + biopsy with cytogenetic testing. The phenotype is ineffective hematopoiesis with a propensity to develop acute myeloid leukemia (AML). It has undergone a number of varied diagnostic criteria and classifications over the years ranging from the French American British (FAB) criteria [1] and the World Health Organization (WHO) classifications in 1999 [2], 2002 [3], 2008 [4], and 2016 [5] (Fig. 1.1). Major differences between the 2008 and 2016 classifications include the replacement of "refractory anemia" with by "MDS" with, the collapsing of "refractory anemia, thrombocytopenia and neutropenia" into "MDS with single lineage dysplasia," and the replacement of "refractory anemia with ring sideroblasts" with MDS with ring sideroblasts (RS) and single lineage dysplasia or multilineage dysplasia (MDS-RS-SLD, MDS-RS-MLD). The international classification of disease (ICD) codes for MDS have evolved over time and they do not encompass all forms of MDS. In the ninth edition of the International Classification of Diseases (ICD-9-CM), MDS was coded as a disease of the blood and blood-forming organs (ICD 238.72–238.75) but was reclassified as a neoplasm in the tenth edition (ICD-10: D46) and the ICD for Oncology Third Edition (ICD-03), the classification system used by population-based cancer registries [6, 7]. When WHO reclassified MDS as a neoplastic disease and ICD-03 was implemented internationally, it became reportable to National Cancer Institute

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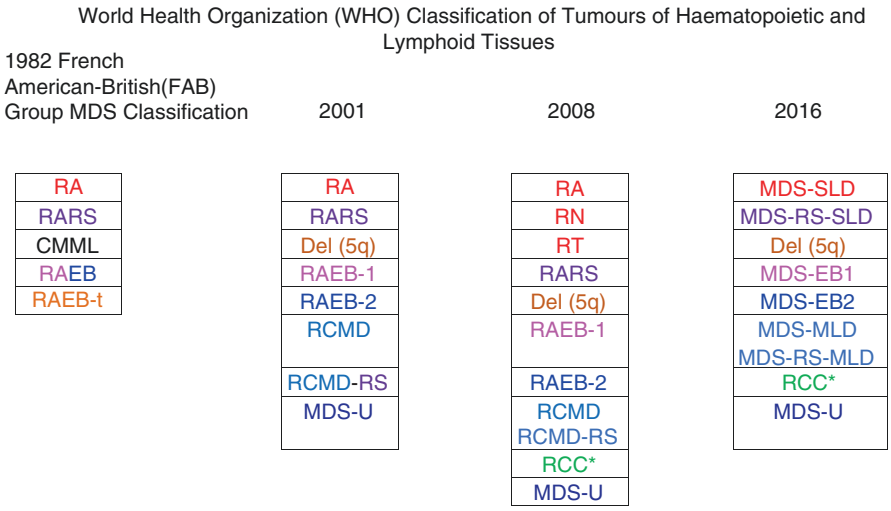

Fig. 1.1 The classification systems for MDS from 1982 to 2016. Entities that encompass the same subtype are color coded. *Legend*: *RA* refractory anemia, *RARS* refractory anemia with ring sideroblasts, *CMML* chronic myelomonocytic leukemia, *RAEB* refractory anemia with excess blasts, RAEB-T refractory anemia with excess blasts in transformation, Del5q MDS with isolated del5q, RAEB-1 refractory anemia with excess blasts type 1, RAEB-2 refractory anemia with excess blasts type 2, RCMD refractory cytopenia with multilineage dysplasia, RCMD refractory cytopenia with multilineage dysplasia and ring sideroblasts, MDS-U MDS unclassifiable, RN refractory neutropenia, RT refractory thrombocytopenia, RCC refractory cytopenia of childhood, MDS-SLD MDS with single lineage dysplasia, MDS-MLD MDS with multilineage dysplasia, MDS-EB1 MDS excess blasts type 1, MDS-EB2 MDS with excess blasts type 2, * provisional. (Adapted from Figure 1 of Zeidan et al. [13])

Surveillance, Epidemiology, and End Results (SEER) Program in 2001 and other cancer registries worldwide. SEER is the authoritative source on cancer incidence and survival in the USA and representing approximately 26.2% of the US population [8]. Using SEER data encompassing the years 2001–2003, US incidence of MDS was first published in 2007 [9] and updated in 2008 with the inclusion of data from North American Association of Cancer Registries (NAACR) which encompasses 82% of the US population [10] and included 24,798 patients with MDS overall. Major findings from both studies included the following: the overall age-adjusted (AA) incidence was 3.3 cases/100,000, this was a disease diagnosed at a median age of 76 with 86% of cases aged ≥60 years, and incidence was increasing dramatically with age (Fig. 1.2); men had a significantly higher incidence rate than women (4.4 versus 2.5 per 100,000/year); (AA) MDS incidence was more common in Caucasian (3.3) than Black (2.4), Asian/Pacific Islander (2.5), and American Indian/Alaska native (1.2) patients; MDS was associated with a 3-year overall and relative survival of only 35% and 42%, respectively. The incident cases (defined by FAB) included 14% refractory anemia (RA), 10% refractory anemia with ring sideroblasts (RARS), 11% refractory anemia with excess blasts (RAEB), 2% refractory anemia with

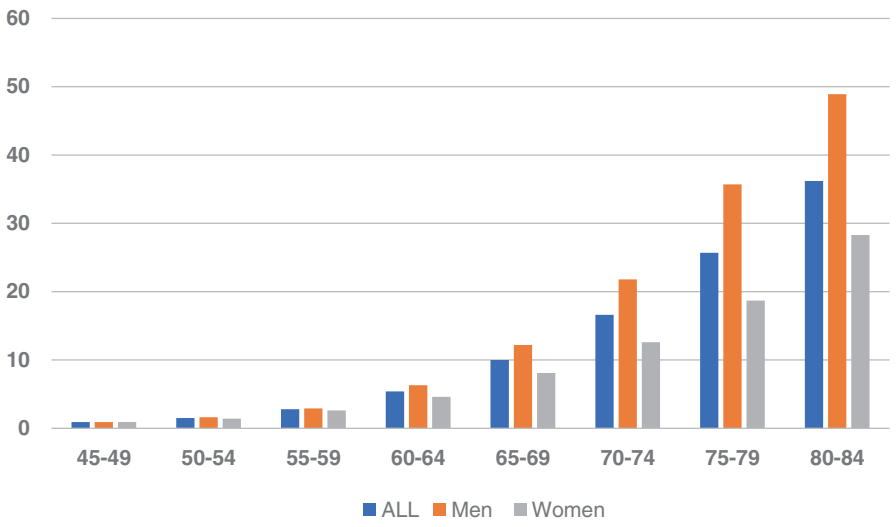

Fig. 1.2 SEER 2001–2003 Incidence/100,000 (*y* axis) according to age categories overall and by sex

excess blasts in transformation (RAEB-T), 2% refractory cytopenia with multi-lineage dysplasia (RCMD), and 2% deletion 5q MDS (del5q). Importantly, 56% incident cases had no MDS subtype specified therefore the observed subtype distribution may not be entirely representative. Incidence increased over the 3 years from 3.3/100,000 in 2001 to 3.8/100,000 in 2004 [10] with an estimated 9700 new cases made in 2004. Increasing incidence after 2001 has been reported by many disease registries [11, 12] and may be a function of increased recognition and reporting in an aging population. Using a SEER November 2017 submission, Zeidan et al. estimated the 2015 incidence to be 4 cases/100,000 with 13,400 new cases of MDS diagnosed annually in the USA [13], suggesting a leveling off in age-adjusted incidence in recent years. The incidence data reported in some other Western countries are summarized in Fig. 1.3 and are very aligned with that of SEER and the North American Association of Central Cancer Registries (NAACR). Differences may relate to sources (registry versus claims-based and chart review), years of case ascertainment, ICD-version codes used, the inclusion or exclusion of entities no longer classified as MDS such as chronic myelomonocytic leukemia (now classified as an overlap MDS/MPN since 2001) or refractory anemia with excess blasts in transformation (now classified as AML in WHO since 2001), or differences in ethnic makeup and population age.

In addition to ICD codes that do not always align with correct or histologically confirmed diagnoses, another significant limitation to relying on cancer registries for disease incidence is their reliance on inpatient reporting. For example, only 4% of the MDS incident cases from NAACR originated from physician's offices [10]. Using a novel, more stringent Medicare claim-based algorithm that looked at blood

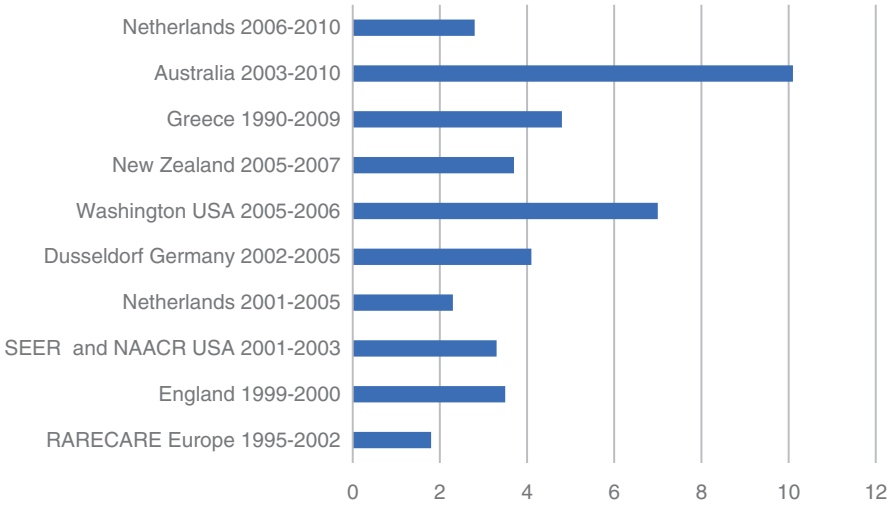

Fig. 1.3 MDS Incidence/100,000 in Western Countries from 1995–2010. *Reference Source Legend:* the Netherlands 2006–2010 [11]; Australia 2003–2010 [27]; Greece 1990–2009 [12]; New Zealand 2005–2007 [75]; Washington, USA, 2005–2006 [76]; Dusseldorf, Germany, 2002–2005 [22]; the Netherlands 2001–2005 [11]; SEER and NAACR, USA, 2001–2003 [10]; England 1999–2000 [77]; RARECARE, Europe, 1995–2002 [78]

work and bone marrow testing applied to beneficiaries residing in a SEER region between 2001–2005, Cogle et al. identified more than 9600 MDS cases not captured by SEER. For 2005, they estimated the MDS incidence to be almost fourfold higher than the SEER incidence in persons 65 years of age or older (75 versus 20 cases/100,000) [6].

A similar underestimation of true MDS incidence was also reported in a population-based linkage study in Australia with the annual incidence for those aged 65 years and older estimated to be 68/100,000 [14]. Despite these higher incidence rates, most experts acknowledge that this likely *still* represents an underrepresentation of true incidence because of either underreporting of pathologically confirmed cases to cancer registries (if not mandated) or the failure to perform diagnostic bone marrows in the investigation of unexplained anemia, a highly prevalent problem in older adults [15]. Supporting this, an interrogation of electronic pathology reports in Florida during 2006 identified that uncaptured cases of MDS by the Florida cancer registry made up 38% of the total true MDS cases. This led to a calculated incidence of 5.3 cases/100,000 (60% higher than SEER) [7]. Using physician billing claims of the ICD-9 code for MDS (not entirely specific to MDS) in 2003, Goldberg et al. identified the incidence to be 162 cases/100,000 with a median age at diagnosis of 77 and 45,000 newly diagnosed cases. During the 3-year follow-up, 73% of 512 patients suffered cardiac events (62% new) with an age-adjusted odds ratio compared with non-MDS Medicare patients of 2.1 (95% CI 1.7–2.5). MDS patients also had an increased prevalence of diabetes, dyspnea, hepatic diseases, and infectious complications. Of interest was a higher 3-year survival rate of

60% compared with 35% of SEER highlighting the potential referral and reporting biases of cancer registries versus community settings or improved supportive care over time [16].

The epidemiology of MDS reported in Asian countries has been reported to differ from North America and Europe. In one study, Chinese patients with MDS (compared with Western patients) were younger at diagnosis (median 49 vs 65–73 years) and had lower percentages of RARS (2.8 vs 6.6–15.3%) and chronic myelomonocytic leukemia (CMML) (5.2 vs 11.7–31%). Similarly, incidences of single chromosome 5 and 7 abnormalities were lower than those in Western countries (2.2 vs 17.8–42.5%) while complex karyotypes were more common (39% versus 16–25%) [17]. These differences have been observed in other Asian countries such as Korea [18] and Japan [19], and younger age (56–61) at diagnosis has also been reported in Thailand, Turkey, and Central Africa in smaller series (review) [20]. In an analysis of the International Working Group for Prognosis of MDS database (IWG-PM) that encompassed 7012 patients, 300 Japanese (JPN), and 5838 Caucasian (CAUC) patients aged >39 years old were compared. JPN patients were 5.5 years younger at diagnosis (65.5 versus 71), had lower rates of RARS (4 vs 12.6%) and del5q (1.3 versus 4.7%), but higher rates of refractory cytopenia with multilineage dysplasia (41 versus 28%). JPN patients had lower hemoglobin (85 versus 99 g/L), platelet counts (75 vs 130 × 10^9/L), and absolute neutrophil counts (1.3 versus 1.91 × 10^9/L) and were less likely to be red blood cell transfusion dependent at diagnosis (25 versus 33%). While cytogenetic risk categories did not differ, there were some differences in selected karyotypic aberrations. CAUC patients were more likely to fall into very low international prognostic scoring system revised (IPSS-R) (19.5 versus 10%) and Low international prognostic scoring system (IPSS) (38.5 versus 20%) risk categories. Time to AML did not differ between ethnic groups but the OS was significantly longer in JPN even adjusted for age, FAB, and IPSS-R categories. The impact of cytopenias on overall survival (OS) and leukemia-free survival (LFS) was lower in JPN but the impact of BM blasts and cytogenetics risk group was higher [21].

Prevalence

Prevalence is harder to quantify and may be increasing with the aging population and the availability of some disease-modifying agents that extend life. In 2003, it was estimated to be 13/10000 in Dusseldorf, Germany [22], and applying comparable numbers to the USA, the prevalence would be estimated to be 42, 600 cases in 2018 [13]. This is probably still an underestimate. Applying assumptions from the national health and nutrition evaluation survey (NHANES) study on anemia, Sekeres et al. estimated there may have been as many as 170,000 prevalent cases in 2010 [23]. If one applied the estimated prevalence of 155 cases/100,000 (derived from private health insurance claims), the estimated prevalence in the USA could be as high as 500,000 cases [24] although not all insurance claims are histologically proven cases of MDS.

Clinical Presentation

The median age at diagnosis ranges from 71–79 years of age [9, 25–27]. MDS is more common in males than females with a male to female sex ratio of 3–4:2, a ratio that increases with age [9].

The disease usually presents with either symptomatic or asymptomatic cytopenias in one or more cell lines. The most common symptoms may include fatigue (55%), fever and infection (15%), or bleeding (8%) [12] as well as dyspnea on exertion or angina. The blood film indices may show macrocytosis, anisocytosis, tear drops, and a dimorphic population in the red blood cells. The leukocytes may demonstrate a left shift, "pelgeroid" neutrophils, and circulating blasts. Lymphadenopathy and splenomegaly are uncommon but may be seen with the MDS/MPN overlap syndromes. Fifty-two percent present with anemia (hgb < 10 g/L), 18% with neutropenia (ANC < 0.8×10^9/L), and 40% with thrombocytopenia (plt < 100×10^9/L) [26], 35% have bicytopenia and 12% pancytopenia [12] at diagnosis.

In the international working group for myelodysplastic syndromes (IWG-PM) project database ($n = 7012$), 32% of patients were transfusion dependent at diagnosis [26]. In a US physician survey that included 670 newly diagnosed patients, only 22% with lower risk disease were dependent on transfusions compared with 68% of higher risk patients [25]. Similarly, 29% of MDS patients in the European Union MDS registry of lower risk MDS patients (EUMDS) were transfusion dependent at diagnosis [28], however, 41% received transfusions within 1 year of diagnosis with transfusion dose density in the first year correlating with progression-free survival [29]. In the Medicare Standard Analytic File study, the 40% of transfusion-dependent MDS patients suffered a higher rate of clinical complications like infections, dyspnea, hepatic events, diabetes, fungal infections, and cardiac events [16].

Survival, Cause of Death, and Leukemia Rates

The median survival of MDS patients ranges from 0.8–8.8 years overall [26] but varies considerably according to age, comorbidities, transfusion dependence, frailty, karyotype, selected mutations, number and depth of cytopenias, and marrow blast percentage. Prognosis for OS and leukemia-free survival (LFS) according to a number of established risk scores will be discussed in detail in a later chapter. Approximately 25–30% of MDS patients develop AML [30] and the excess mortality in MDS appears to be driven primarily by non-leukemic factors [31]. Three and 5-year overall survival rates are 42% and 29%, respectively [32], and the 3-year relative survival of MDS patients compared with age matched controls is only 45% [10]. Where known, the leading causes of accelerated death in Germany were AML (47%), infection (27%), bleeding (10%), and cardiovascular disease (8%) [30]. Using SEER data from 2001–2011, the most common cause of death in >21,000 patients were MDS/leukemia (50%), cardiovascular disease (19%), infection (5%),

and other (11%) with cardiovascular disease cause of death rates matching that of MDS/leukemia after 5 years [33]. Despite the advent of some disease-modifying agents, the overall survival in MDS has not convincingly improved since 2001 [11, 31, 34].

Association of MDS with Autoimmune Diseases

Autoimmune and inflammatory conditions (AICs) are observed in 7–28% of patients with MDS and may precede, coincide, or follow the diagnosis of MDS [35, 36]. This is not surprising since some of the same immune perturbations that result in AICs (inflammatory cytokines, autoantibodies, increased T regulatory cells, and myeloid-derived suppressor cells) or the treatments to suppress them may contribute to the pathogenesis of MDS. Having an AIC may increase the risk of developing MDS (OR 1.5–2.0) [37, 38] possibly due to chronic immune stimulation although one cannot discount the potentiating or causal effects of anti-inflammatory/immunosuppressive agents used to treat the AIC or a common genetic or environmental susceptibility to both. There may be usually a short latency between AIC and MDS [39] and some but not all studies have found AICs to be more common in younger MDS patients and those with higher risk disease [35]. The AICs associated with MDS span polyarthritis, neutrophilic dermatosis (Sweet's syndrome), connective tissue diseases, vasculitis, hypothyroidism, immune thrombocytopenia purpura (ITP), psoriasis, and autoimmune hemolytic anemia. In a pooled retrospective analysis from Moffit and Kings College Hospital of 1408 patients, 27% had an AIC, the most common being hypothyroidism (44%), ITP (12%), and rheumatoid arthritis (11%). MDS patients with AIC in this series were comprised disproportionately of women (44%), associated more with RCMD, and were less likely to be RBC transfusion dependent. In addition, MDS with AIC had improved overall survival compared with those without (median OS 60 mos. versus 45 mos., $p = 0.011$) even adjusting for IPSS-R and age [40]. However, other smaller studies have either found no effect or inferior OS for MDS patients and AICs [35, 41].

Risk Factors for MDS

Age is one of the biggest risk factors for the development of MDS. One contributing factor may be the acquisition of genetic mutations during aging in hematopoietic stem cells that provide a clonal proliferative advantage but without cytopenias or dysplasia. This phenomenon, deemed age-related clonal hematopoiesis (ARCH) or clonal hematopoiesis of indeterminate potential (CHIP), is observed in 10% of the general population above the age of 60–65 and increases with age. CHIP is associated with an increase in risk of hematologic cancer (HR 11.1–12.9) [42, 43]. Since MDS is a clonal disease whose pathophysiology is linked to chromosomal

abnormalities and somatic mutations in genes that regulate methylation, differentiation, cell signaling, RNA splicing, nuclear transcription, and proliferation, the increased prevalence with age of somatic mutations in genes regulating some of these pathways may explain the higher incidence of MDS with age. This subject is discussed in detail in a later chapter.

In addition, there are hereditary germ-line mutations and syndromes associated with the development of MDS [44] that will be discussed in a later chapter.

A number of occupational, environmental, and lifestyle factors have been associated with MDS.

Pesticide exposure Pesticide exposure appears to be a risk factor for AML in manufacturing workers and pesticide applicators [45], but is this finding applicable to MDS? Because of conflicting case control studies, a large meta-analysis based on 1942 cases and 5359 controls was conducted and included 11 retrospective case-control studies from USA, Italy, UK, France, Serbia, China, and France published between 1990 and 2011. The findings were as follows: A) pesticide exposure was associated with a 95% increased risk of MDS. B) Subgroup analyses showed a stronger effect of pesticide exposure on RA/RARS than on RAEB/RAEB-t with exposed MDS patients having a 63% increased risk of RA/RARS (95% CI 1.06–2.51) and 49% increased risk of RAEB/RAEB-T, respectively (95% CI 0.78–2.84). C) The risk from pesticides was primarily due to exposure to insecticides (OR 1.71, 95% CI 1.22–2.4), not herbicides (OR 1.16, 95% CI 0.55–2.43) and fungicides (OR 0.7, 95% CI 0.2–3.2). D) The adverse effect of pesticide exposure on MDS was observed in Europe (OR 2.13, 95% CI 1.35–3.36) and Asia (OR 2.0, 95% CI 1.17–3.41) but not in the USA (OR 1.52, 95% CI 0.3–7.73) [46].

Obesity and Lifestyle Factors

A prospective cohort study of the national institutes of health (NIH) and the American Association of Retired Persons (AARP) examined the relationship between diet, body mass index (BMI), exercise, and smoking on the development of MDS incident cases identified through state cancer registry databases. Across the USA, 470,000 men and women between the ages of 50–71 were included and 193 incident cases of MDS were identified. Obesity (BMI $\geq$ 30) was associated with a greater than twofold increased risk of MDS and there was a significant positive trend for the relation between BMI and MDS. Physical activity (vigorous physical activity $\geq$3 times/week) had a protective effective effect on MDS development (HR 0.68, 95% CI 0.49–0.95) compared with physical inactivity ($\leq$ 3 x/month). Neither alcohol consumption, fruit and vegetable intake, nor meat intake were associated with MDS [47]. In a meta-analysis of five case-control studies, alcohol consumption was also not significantly associated with MDS [48].

Benzene

Benzene is a volatile organic compound most commonly used for the manufacturing of plastic packaging, insulation, and other products. It is one of the top 20 chemicals produced in the USA, occurs naturally in petroleum products and premium gasoline, and occupational exposure to benzene by inhalation or dermal absorption spans many industries [49]. It is carcinogenic and myelotoxic [50] and its association with acute leukemias is well known for many years [51]. One large hospital-based case control study from China demonstrated a direct exposure-response pattern (threshold >3 parts per million) with refractory cytopenias and multi-lineage dysplasia the most common type of MDS in China [52]. Ambient air exposure to benzene may also be important since it derives from many sources such as automobile emissions, burning wood, cigarette smoke, mining, and many others. Using data from the environmental protection agency (EPA) national air toxics assessment (NATA) program, Teras et al. modeled census tract ambient benzene concentration estimates to examine potential associations with hematologic cancers in a large prospective cohort (n = 115,996) between 1997 and 2013. They found that total ambient benzene was associated with MDS (HR 1.16, 95% CI 1.01–1.33 per $\mu g/m^3$), follicular lymphoma (in men), and T cell lymphomas [49]. In another study, latency (<10 years) from last exposure, total length of occupational exposure (2–10 years), and younger age at first exposure (age < 30) also influenced the associations between benzene and MDS/AML [53]. The conclusive associations between benzene exposure and MDS has been recently expertly reviewed [54].

Smoking

Interestingly, smoking, a significant source of benzene exposure, was not positively associated with all MDS or RCMD in the Chinese study highlighted above [52] but showed associations with RAEB and refractory anemia among men in Japan with a HR for current smokers relative to never smokers of 2.11 (95% CI 0.9–4.9) [55]. The largest meta-analysis of 10 case-control studies evaluating 1800 cases and 2000 controls found an overall risk of 1.45 (95% CI 1.2–1.7) with ever smoking [48]. In the only prospective cohort study of the NIH/AARP, former smokers (HR 1.68, 95% CI 1.17–2.41) and current smokers (HR 3.17, 95% CI 2.02–4.98) had significantly elevated risks of MDS, with the highest risk in those currently smoking more than 1 pack of cigarettes/day (HR 4.70, 95% CI 2.68–8.24) [47]. In one study, patients with chromosomal abnormalities were more likely to be ever smokers (OR 1.92) than patients with normal karyotype [56], and in another study, poor risk karyotypes such as chromosome 7 abnormalities were more associated with smoking as well [57].

Therapy-Related MDS

MDS is deemed therapy related if it follows treatment with cytotoxic chemotherapy or irradiation and is classified as a therapy-related myeloid neoplasm in the WHO classification and is combined with T-AML and T-MDS/myeloproliferative neoplasms (MPN) due to similar prognostic and genetic profiles [4]. T-MDS patients tend to be younger (median age 68), and have a higher proportion of IPSS-R high risk scores compared with primary MDS, have short time to progression to overt AML, and median survivals of 16 months [58].

Therapy-related MDS comprises 10–15% of MDS cases [10, 25] and is associated with karyotypic abnormalities 85–90% of the time (compared with 45–50% in de-novo MDS) [59]. The most frequent primary diseases are non-Hodgkin's lymphoma (28%), breast cancer (16%), myeloma (6%), prostate cancer (96%), Hodgkin's lymphoma (5%), and gastrointestinal tumors with preceding chemotherapy in 75% and radiotherapy in 47%. The most common chemotherapeutic drugs received included alkylating agents (65%), topoisomerase inhibitors (44%), antitubulin agents (26%), and antimetabolites (26%) [58]. In a nation-wide nested case control study from Taiwan of 6300 cancer patients, the adjusted odds ratios for developing MDS after radiotherapy and chemotherapy were 1.53 (95% CI 1.33–1.77) and 1.51 (95% CI 1.25–1.82), respectively, and there was an interaction effect when both chemotherapy and radiotherapy were administered [60]. Radiation has also been linked with increased risk of MDS in a number of tumors including breast cancer [61, 62], prostate cancer [63], lymphoma [64, 65], and thyroid cancer [66], although the absolute increased risks are often small . After involved field radiotherapy, the risk appears to peak at 2 years and normalize after 10–15 years [67].

MDS that develops after exposure to alkylating agents (cyclophosphamide, melphalan, chlorambucil, etc.) often has a latency of 5–10 years and is associated with deletions and unbalanced translocations affecting chromosome 5 and 7 or complex karyotypes, often with associated *TP53* mutations. MDS that develops after exposure to topo-isomerase-2 inhibitors (adriamycin, topotecan, etoposide) is less common, occurs earlier (2–3 years), and is associated with an mixed lineage leukemia (MLL) translocation at 11q23 or RUNX1/AML1 at 21q22 [68]. T-MDS is also linked with exposures to nucleoside analogs (e.g., fludarabine) [69] and anti-metabolites (Imuran) [68, 70]. ARCH or CHIP may also be linked to T-MDS possibly due to the clonal selection advantage upon bone marrow reconstitution post chemotherapy. This is relevant for both lymphoma [71] and solid tumor patients [72, 73] and has been linked with pretreatment *TP53* and PPM1D mutations [72]. The risk of T-MDS/AML post autologous stem cell transplant (ASCT) ranges from 1% to 20% and has been associated with cumulative doses of alkylating agents, total body irradiation, graft source, and preparative regimens [64], so it is notable that clonal mutations were found in the stem cell product in 67% of the 12/401 patients with non-Hodgkin's lymphoma who underwent an ASCT and went on to develop a therapy-related myeloid neoplasm (TMN) [74]. The 10-year cumulative incidence for T-MN was 14.1% vs 4.3% for those with and without clonal mutations, respectively; $P = 0.002$.

Summary

MDS is a heterogeneous clonal bone marrow malignancy diagnosed primarily in older patients aged 71–76 with an age-adjusted incidence derived from cancer registries of 4–5 cases/100,000 that increases tenfold above the age of 80. Incidence and prevalence have increased since its initial definition as a disease in 1982 primarily due to better recognition, investigation of anemia, the availability of therapies, and the aging population. These data are likely significant underestimates since incidence data derived from chart reviews and reimbursement claim databases are significantly higher. MDS is more common in men and Caucasians. The expected survival of an MDS patient is curtailed by >50% due to disease-related complications that include acute myeloid leukemia, infections, bleeding, and cardiovascular disease and is dominated by non-leukemic causes. The WHO classification of MDS has undergone three revisions over a 15-year period, is continuously evolving, and is currently based on the degrees of bone marrow dysplasia, blast %, the presence of ring sideroblasts, and karyotype. While age is the biggest risk factor, environmental exposures to radiation, pesticides, benzene, and lifestyle factors that include smoking, obesity, and physical inactivity have been associated with higher rates of MDS. Exposure to mutagenic chemotherapy and radiotherapy is associated with therapy-related MDS, a devastating condition that accounts for 10–15% of all MDS and is expected to rise in prevalence as the population ages and the number of cancer survivors increase. Finally, age-related clonal hematopoiesis and selected germ line mutations are also risk factors for the development of de-novo and T-MDS.

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