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Hematological Disease

Myelodysplastic Syndromes in Older Adults

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Myelodysplastic syndromes (MDS) are among the most common hematological malignancies in Western countries, with a median age at diagnosis of 74. They are a stem cell disorder characterized by cellular dysplasia, cytopenias, and an increased risk of transformation to acute myeloid leukemia. Disease trajectory is commonly determined by the international and world prognostic scoring systems (International Prognostic Scoring System and the World Health Organization [WHO] classification–based prognostic scoring system) and the WHO classification. Some patients have an indolent disease course, while others experience a rapid deterioration and short overall survival. For many years, the mainstay of therapy was supportive care with blood transfusions and hematopoietic growth factors. Fortunately, novel effective agents including lenalidomide, hypomethylating agents, and oral iron chelators have emerged over the past 5–10 years that improve transfusion dependence and may alter the natural history of the disease. These new therapeutic options offer new hope for individuals with MDS and bolster the role for the investigation of unexplained cytopenias in the older patient.

Key words: *myelodysplastic syndrome, erythropoietin, anemia, red blood cell transfusions, stem cell disorder*

Introduction: What Are the Myelodysplastic Syndromes?

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, cellular dysplasia, peripheral cytopenias, and an increased risk of transformation to acute myeloid leukemia.[1] The majority of people with MDS present with anemia, which is usually macrocytic in nature. However, other presentations may include unexplained neutropenia, thrombocytopenia, or infections.[2] The cytopenias may be chronic in nature and detected incidentally on routine blood work, or patients may be symptomatic with fatigue, dyspnea, angina, and increased bruising and bleeding.

Who Gets Myelodysplastic Syndromes and How Common Are They?

Older adults are primarily affected by MDS, with a median age at diagnosis of 74 years.[3] The incidence of MDS increases substantially with age and is more common among males than females (Figure 1).[4] Most clinicians agree that the reported incidence figures represent a gross underestimation of the true disease burden since many older adults with unexplained anemia are never referred to hematologists for diagnostic evaluation. Using the prevalence of unexplained anemia in older adults, the prevalence of MDS in the U.S. has been estimated to be as high as 63 in 100,000.[5] Based on our analysis of bone marrow examinations for unexplained cytopenias at Sunnybrook Health Sciences Centre, we speculate that MDS prevalence may be as high as 10,629 cases in Canada or 246 in 100,000 Canadians >65 years.[6] Myelodysplastic syndromes develop de novo 90% of the time but may develop after mutagenic chemotherapy or radiotherapy (often with complex or poor-risk cytogenetics) in 10% of cases.

How Are Myelodysplastic Syndromes Diagnosed and Classified?

A bone marrow aspirate and biopsy are necessary to make a definitive diagnosis of MDS. The marrow is usually hypercellular or normocellular despite the patient being cytopenic. This paradox is explained by ineffective hematopoiesis and increased apoptosis in the bone marrow, resulting in decreased mobilization of myeloid cells to the peripheral blood. Hypocellular MDS may be found in a minority of cases and may be confused with aplastic anemia. Bone marrow samples must show dysplastic changes in at least 10% of the cells in one or more lineages (neutrophil and/or erythroid precursors and/or megakaryocytes).[7] It is important to determine whether bone marrow dysplasia is primary (due to a clonal disorder) or secondary. Secondary causes of dysplasia include vitamin B_{12}/folate deficiency, severe infections, active autoimmune diseases, hypothyroidism, exposure to heavy metals, chronic alcohol use, and the use of certain drugs (granulocyte colony-stimulating factor [G-CSF], chemotherapy, co-trimoxazole, and others).[8] In these instances, the diagnosis of MDS may be

**The Odette Cancer Centre is a "Centre of Excellence" for MDS clinical and translational research. Referrals to new patient bookings of patients with suspected or confirmed MDS are welcome and can be made by faxing a referral to 416-480-6179, attention MDS clinic.*

Table 1: Baseline Investigations for Workup of Suspected Myelodysplastic Syndromes or Unexplained Macrocytic Anemia

Complete blood count with differential
Blood film
Reticulocyte count
Renal profile
Liver profile
Vitamin B12 and red blood cell folate
Ferritin and iron saturations
Thyroid-stimulating hormone
Serum erythropoietin level

difficult; however, the chronicity and severity of progressive cytopenias may sometimes convert a suspected MDS to confirmed. In our experience, 50% of those with suspected MDS declare themselves as a confirmed myeloid malignancy over the next few years.[6] Cytogenetics are essential at the time of bone marrow biopsy for confirmation of the diagnosis in equivocal cases, and for prognosis. Table 1 lists baseline investigations that should be completed in the workup of suspected MDS or an unexplained macrocytic anemia.

The most recent classification of MDS was published by the World Health Organization (WHO) in 2008 (Table 2).[7] Based on this classification system, low-risk MDS include refractory cytopenias with unilineage dysplasia (RCUD), refractory anemia with ringed sideroblasts (RARS), refractory cytopenias with multilineage dysplasia (RCMD) and MDS with isolated deletion 5q (del[5q]), whereas refractory anemia with excess blasts-1 (RAEB-1) and RAEB-2 constitute high-risk MDS.

What Is the Prognosis in Myelodysplastic Syndromes?

The International Prognostic Scoring System (IPSS) was devised as a means to estimate patient survival and risk of progression to acute myeloid leukemia. Prognosis is determined by a weighted scoring system using the number of cytopenias, bone marrow blast percentage, and cytogenetics (Table 3).[9] Four risk categories are identified: low, intermediate-1, intermediate-2, and high risk. Median survival ranges from 0.4 –5.7 years which is independent of age at diagnosis. Approximately two thirds of patients fall into the lower-risk categories at diagnosis.

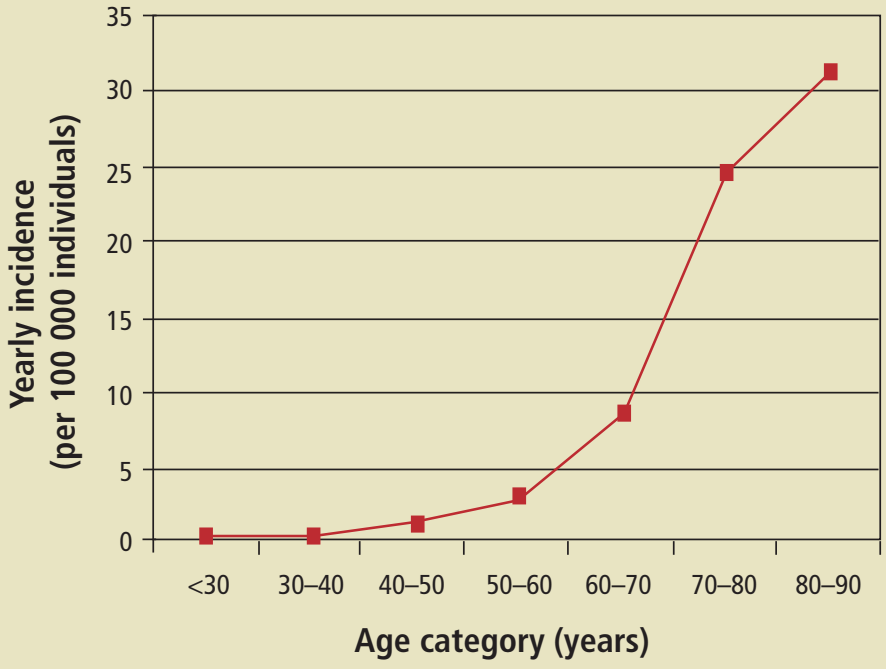
The IPSS is useful in determining prognosis at diagnosis; however, it is not time dependent and does not include transfusion dependency. In recent studies, transfusion dependency has been shown to be independently associated with inferior survival in patients with MDS.[10,11] A new scoring system—the WHO classification–based prognostic scoring system (WPSS)—uses WHO category, cytogenetic risk group, and red blood cell (RBC) transfusion requirement to determine prognosis.[12] Five risk categories are identified: very low, low, intermediate, high, and very high, for which the median survival and risk of progression to acute myeloid leukemia at 5 years is, respectively, 140 months and 3%, 66 months and 14%, 48 months and 33%, 26 months and 54%, and 9 months and 84%.[12]

The advantages of the WPSS include the identification of patients within the low-risk subgroups with an adverse prognosis, its inclusion of transfusion requirement as an independent negative prognostic variable, and the ability to determine patients' prognosis throughout their disease course and at time of progression. By using these scoring systems, the prognosis of an individual patient can be determined to assist in the selection of appropriate therapy.

How Do Patients with Myelodysplastic Syndromes Fare Compared with Age-Matched Controls?

Individuals with MDS have 50% of the survival of age-matched controls.[13] Among lower-risk individuals, non-leukemic causes of death predominate, while among higher-risk persons, the opposite holds true.

Figure 1: Incidence of Myelodysplastic Syndromes Increases with Age



Source: Jadersten M and Hellstrom-Lindberg E, 2009.[21] Used by permission of Wiley-Blackwell.

Nonleukemic death is caused primarily by infection and excessive cardiac disease.[14] The increased cardiac disease may be attributed to chronic anemia and the resultant cardiac remodelling[15] and transfusion-associated hemosiderosis. The increased comorbidities of the older adult with MDS[16] no doubt exaggerate the detriments of anemia and transfusion dependence.

How Are Myelodysplastic Syndromes Treated?

Apart from allogeneic bone marrow transplantation, MDS is an incurable disease. In the past, the standard treatment was supportive care, consisting of RBC/platelet transfusions and antibiotics for infection.[17] Today, there are several effective therapies that are dependent on the individual's MDS risk category, cytogenetics, comorbidities, and age.

Treatment of Low-Risk Myelodysplastic Syndromes

Among patients with lower-risk IPSS scores, the main goal of therapy is to improve quality of life (QOL). Mitigating transfusion dependence and preventing complications of blood transfusions can achieve this improvement.

Anemia and Transfusion Therapy in Myelodysplastic Syndromes

Anemia is present at diagnosis or appears during the disease course in >80% of patients.[18] Anemia is a risk factor for mortality and morbidity in older adults and is predictive of increased hospitalization, physical decline, and disability.[19] Interestingly, borderline/low-normal hemoglobin levels (120–130 g/L) have also been associated with increased mortality and physical decline in older adults.[20,21] However, there are currently no data supporting treatment in these individuals.

The majority of individuals with MDS require RBC transfusion support during the course of their disease.[18,22] Red blood cell transfusion dependence is associated with significant clinical, economic, and QOL consequences.[22,23] There is no standard hemoglobin thresh-

Table 2: World Health Organization 2008 Classification of Myelodysplastic Syndromes

Disease	Blood Findings	Bone Marrow Findings
Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anaemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	Unicytopenia or bicytopeniaa No or rare blasts (<1%)	Unilineage dysplasia; ≥10% of the cells of the affected lineage are dysplastic <5% blasts <15% of the erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only <5% blasts ≥15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%) No Auer rods <1 x 10^9 L^{-1} monocytes	Dysplasia in ≥10% of cells in two or more myeloid lineages <5% blasts No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods <1 x 10^9 L^{-1} monocytes	Unilineage or multilineage dysplasia 5–9% blasts No Auer rods
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts (<1%) No Auer rods	Unequivocal dysplasia in <10% of cells in one or more myeloid cell lines <5% blasts
MDS associated with isolated del (5q)	Anaemia No or rare blasts (<1%) Platelet count usually normal	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts

Source: adapted from Swerdlow S *et al.*, 2008.[7]

old for transfusion; each patient's need must be assessed on an individual basis. Generally, patients are transfused with RBCs if they have anemia-related symptoms such as dyspnea, fatigue, or chest pain. Once transfusion dependence begins, the intervals between transfusions typically shorten over time. Patients who are transfusion dependent should have regular complete blood count assessments and prescheduled transfusion medicine appointments to avoid visits to the emergency department with critically low hemoglobin values.

Not surprisingly, people with MDS who have anemia or are transfusion dependent have inferior health-related QOL scores compared with an age- and sex-matched healthy population.[24] Reductions in QOL domains are associated with a hemoglobin of <107 g/L,[15] excessive fatigue,[25] and transfusion dependence.[26] Contrarily, drugs that improve hemoglobin levels are associated with increases in QOL scores.[27,28]

Alloimmunization, volume overload, and transfusion-related iron overload are serious and common complications of chronic RBC transfusions. End-organ oxidative damage can ensue, affecting the heart, liver, and endocrine organs. In addition to transfusion-related iron overload, people with MDS have increased intestinal absorption of iron and may show evidence of iron loading even prior to the initiation of transfusions.[29] In a retrospective analysis, iron overload in low-risk patients with MDS who have a ferritin level of >1,000 μg/L (1,000 ng/mL) have a decreased overall survival and potentially a decreased leukemia-free survival.[11,30] The effectiveness of iron chelation in reversing organ damage due to iron overload among individuals with MDS has been demonstrated in uncontrolled studies.[31,32] Three iron-chelating agents are available: deferoxamine, deferasirox, and deferiprone. Deferoxamine, administered via subcutaneous (SC) infusion over 10–12 hours per day, has been in use for many years; however, patient adherence is poor. Deferasirox, a new oral iron chelator, has been shown to be safe and effective for individuals with MDS.[33] Adverse effects, of which most are mild to moderate, include diarrhea (most common), gastrointestinal disturbance (nausea, abdominal pain), rash, and elevated creatinine. In accordance with Canadian consensus published guidelines, iron chelation should be offered to MDS patients who are transfusion dependent with an IPSS score of low or intermediate-1, ferritin >1,000 μg/L, life expectancy >1 year, or candidates for allogeneic bone marrow transplantation.[34]

Table 3: International Prognostic Scoring System

Prognostic Variable	0 Points	0.5 Points	1.0 Point	1.5 Points
No. of cytopenias*	0–1	1–2	–	–
Karyotype†	Good	Intermediate	Poor	–
Bone marrow blasts (%)	<5	5–10	–	11–20

Risk Group	Total Score	Median Survival (y)	25% AML Evolution (y)
Low	0	5.7	9.4
Intermediate-1	0.5–1.0	3.5	3.3
Intermediate-2	1.5–2.0	1.2	1.1
High	≥2.5	0.4	0.2

AML = acute myeloid leukemia.
*Cytopenias: hemoglobin <100 g/L, platelets <100 x 10^9/L, absolute neutrophil count <1.8 x 10^9/L.
†Cytogenetics: good = normal, -Y, del(20q); poor = ≥3 abnormalities, chromosome 7 abnormalities; intermediate = all others

Source: adapted from Greenberg C *et al.*, 1997.[9]

Hematopoietic Growth Factors

Hematopoietic growth factors such as erythropoietin (EPO), darbepoetin, and G-CSF are often the first line of treatment for individuals with low-risk MDS. Randomized studies have shown EPO to be superior to placebo in reducing transfusion requirements and improving QOL.[18,35,36] Recently published data have also shown an association between EPO treatment and improved survival.[37,38]

A predictive model is used to identify which patients have the highest likelihood of response (a reduction in transfusion requirement by at least 50% or an increase in hemoglobin by 10 g/L)

Table 4: Prediction Model for Response to Erythropoietin and G-CSF in MDS

Variable	Value	Score	Value	Score
Transfusion need	<2 U/mo	0	≥2 U/mo	1
Serum EPO	<500 IU/L	0	≥500 IU/L	1

Predictive Group	Total Score	Response Rate (%)
Good	0	74
Intermediate	1	23
Poor	2	7

EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; MDS = myelodysplastic syndromes.

Source: Adapted from Hellstrom-Lindberg E *et al.*, 1997.[39]

to EPO and G-CSF (Table 4).[39] Those patients with a serum EPO level of <500 IU/L or who have required two units or less of blood per month have a 74% chance of response. By contrast, patients with a serum EPO > 500 IU/L and who require more than two units of RBCs per month have only a 7% chance of responding to growth factors. Response times vary and can take >8 weeks; the median response duration in responders is approximately 2 years. The recommended starting dosages of erythropoietin are 40,000 U/wk SC, and this can be increased to 60,000 U/wk SC in the absence of a response. The addition of G-CSF (75–300 μg SC three times a week) to EPO increases the response rate by approximately 15–20%.[40]

Lenalidomide

Lenalidomide is an immunomodulatory drug derived from thalidomide that is highly effective in reducing RBC transfusion needs in the 10% of MDS patients with del(5q). In this patient group, lenalidomide can achieve RBC independence in 67% of patients and complete cytogenetic remissions in 45%.[41,42] Lenalidomide is also effective in non-del(5q) MDS, with 26% of low-risk patients achieving transfusion independence.[43] Side effects of treatment included neutropenia and thrombocytopenia in approximately 50% of patients.

Other Treatments for Low-Risk Myelodysplastic Syndromes

In some patients, MDS is caused by autoimmune destruction of hematopoietic precursors. Immunosuppressive therapies such as cyclosporine and antithymocyte globulin have been shown to be effective in a subset of individuals with MDS. A study from the National Institutes of Health identified age <60 years, human leukocyte antigen (HLA)-DR15 phenotype, and minimal transfusion requirements as predictive of response to immunosuppressive therapy.[44] Antithymocyte globulin is an intravenous therapy that must be administered in a monitored setting, given the high rates of serum sickness and infusional reactions. It is rarely offered to patients above the age of 60 years.

New drugs that target aberrant epigenetic changes in the MDS clone (reversible silencing of genes such as tumour suppressor genes, etc.) are also effective in selective lower-risk MDS patients. These include hypomethylating agents such as 5-azacitdine (5-AZA), decitabine, and the histone deacetylase inhibitors vorinostat and valproic acid. In a randomized phase 2 study, 5-AZA engendered transfusion independence in 50–60% of low-risk MDS patients.[45]

Treatment of High-Risk Myelodysplastic Syndromes

The goals of treatment for individuals with high—risk MDS include preventing the development of leukemia, improved survival, and QOL. The only curative treatment for MDS is allogeneic stem cell transplantation which is an option in high-risk patients who are <70 years of age. Very few older adults are candidates for transplantation because of comorbidities and age >70 years.

The hypomethylating agents (5-AZA and decitabine) represent the mainstay of therapy in the absence of a clinical trial. In a randomized study compared with best standard care, 5-AZA was shown to delay the onset of leukemia, provide transfusion independence in 45% of patients, improve overall survival, and decrease the rate of infections.[46] Decitabine is also effective in patients with high-risk MDS; however, it has not been shown to improve survival. The agent 5-AZA is pending Health Canada notice of compliance but is approved for use via the special access program for patients with higher-risk MDS.

Traditional chemotherapeutic agents are uncommonly used in high-risk MDS as remissions are rarely durable and the treatment is often toxic among older adults.

Conclusion

Myelodysplastic syndromes are relatively common diseases in older individuals and should be considered as causes of unexplained cytopenias. In North America, the population over the age of 65 years is speculated to double by the year 2030. With more people surviving cancer after treatment with chemotherapy or radiation, we can expect to see an increase in MDS prevalence. Anemia and transfusion dependence are the most

Key Points

Myelodysplastic syndromes (MDS) are fairly prevalent disorders in older adults and are likely underdiagnosed. A definitive diagnosis can only be made by a bone marrow aspirate/biopsy and cytogenetic studies.

The prognoses for survival and risk of leukemia are determined by the karyotype, the number of cytopenias, bone marrow blast percentage, and transfusion dependence.

Treatment options are determined by the MDS risk group. The goals of therapy in patients with lower-risk MDS are to improve quality of life and eliminate the need for transfusions. The goals of therapy in those with higher-risk disease are to decrease transfusion need, decrease the risk of progression to acute myeloid leukemia, and improve survival. Improving quality of life is important in all patients.

Red blood cell transfusions remain a mainstay of treatment and should be offered to all patients with symptomatic anemia. The optimal hemoglobin threshold is individualized.

Hematopoietic growth factors such as erythropoietin (EPO) and granulocyte colony-stimulating factor are effective in reducing the need for transfusions and improving quality of life in patients with serum EPO levels <500 IU/L and less than two units of red blood cells per month.

Clinical Pearls

Any patient with unexplained cytopenias or macrocytosis should be referred to a hematologist with expertise in treating myelodysplastic syndromes (MDS) for diagnosis and therapy.

Patients with MDS who have lower-risk disease and symptomatic anemia may be offered hematopoietic growth factors and/or lenalidomide if they harbour a deletion 5q clone. Patients with MDS who have higher-risk disease should be offered participation in a clinical trial or treatment with hypomethylating agents, if available.

common clinical complications of MDS, and it is important to recognize that new therapies directed by risk category, performance status, and patient preference are available today. These therapies include hematopoietic growth factors, lenalidomide, immunosuppressive therapy, hypomethylating agents, and others, which have already begun to show improvements in patient outcomes, including overall survival.

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Dr. Buckstein has received honoraria for talks and participation in the advisory board of Roche, Celgene, and Novartis.

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