Myelodysplastic syndromes

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What is MDS?

Myelodysplastic syndromes (MDS) constitute a heterogeneous group of malignant stem cell disorders characterized by dysplasia of myeloid progenitors and their progeny. This results in ineffective hematopoiesis caused by excess proliferation, impaired maturation and excess apoptosis (programmed cell death). This results in peripheral cytopenias, and an increased risk for leukemic transformation.

MDS affects primarily the elderly. Median age at presentation is roughly 70 and is more common in men than women, but less common in Asians and Pacific Islanders.

How does MDS present?

MDS presents primarily with cytopenias, most typically with macrocytic anemia with or without neutropenia and/or thrombocytopenia. In some cases, the progressive decline in hemoglobin, increased mean corpuscular volume (MCV) or red cell distribution width (RDW) may be traced over more than five preceding years. The cytopenias may be asymptomatically detected on routine blood work or may be symptomatic with fatigue, dyspnea, angina, increased bruising and bleeding being the most common symptoms.

How common is MDS?

MDS incidence is 2.2 cases/100,000 in the general population, but rises to 35 cases/100,000 above the age of 80. The estimated prevalence is suspected to be 3,500 to 5,500 cases in Canada although most acknowledge that this is a gross underestimate due to the lack of referrals of elderly patients for the investigation of unexplained cytopenias and the paucity of diagnostic bone marrows in the work-up of unexplained cytopenias in the elderly.

What causes MDS?

Eighty percent of the time, there are no identified causes for the malignant transformation of a stem cell. Mutagens such as radiation and alkylator chemotherapy agents are risk factors in select patients who are diagnosed with therapy-related MDS. Exposures associated with increased risk of primary MDS include smoking, agricultural chemicals and organic solvents.

How is MDS diagnosed?

MDS is a morphological diagnosis that requires a bone marrow aspirate and biopsy to definitively diagnose. Clues may be gleaned from the peripheral blood reports of oval macrocytes, pseudo-Pelger Huet cells, basophilic stippling or a dimorphic population. Cytogenetics are essential at the time of bone marrow for confirmation of diagnosis in equivocal cases and for prognosis. It is important to know that dysplastic hematopoiesis may also be observed in cases of severe infection, HIV, active autoimmune diseases, vitamin B12 or folate deficiency, and hypothyroidism. In these instances, the diagnosis of MDS may sometimes be difficult, although the chronicity and severity of progressive cytopenias may sometimes convert a "suspected" MDS to confirmed.

What is MDS prognosis?

Median survival with MDS ranges from 0.4 years to 5.7 years. Prognosis is determined by the international prognostic scoring system (IPSS)—a weighted scoring system determined by the number of cytopenias (1 versus > 1), bone marrow blast percentage (< 5%, 5–10%, 11–20%, 21–30%), and cytogenetics (good, intermediate and poor). Recently, new prognostic scoring systems have added red blood cell transfusion dependence (WPSS) and iron overload as independent negative prognostic markers for death and leukemia in addition to the traditional IPSS variables.

What is the natural history for MDS?

The natural history varies, but typically involves progressive cytopenias over months to years and 50% of patients will become transfusion dependent of red blood cells and/or platelets. Once transfusion dependence begins, the intervals between transfusions typically shorten. On average, patients receive two units every month, but there should be no standard hgb threshold for transfusion. Roughly 33% of patients will develop acute myeloid leukemia and this is more likely to occur with higher IPSS scores. The remaining two-thirds of patients succumb prematurely compared with age-matched controls from infection, bleeding, iron overload or cardiac failure.

Why iron overload?

Normal iron flux each day is 1–2 mg. Each unit of blood contains approximately 200 mg of iron. When the ability of the body to safely store or carry iron is exceeded, free non-transferrin bound iron causes oxidative damage to tissues in the liver, heart and endocrine glands. This occurs after a total body iron burden of 7–15 grams or roughly 20 to 50 red blood cell transfusions. MDS patients with iron overload have shorter survivals, greater cardiac morbidity and a greater propensity to develop acute myeloid leukemia independent of prognostic scores.

How is MDS treated?

Historically, MDS was considered an incurable disease whose main treatment was supportive care (red blood cell and platelet transfusions, antibiotics). Today, there are several effective therapies.

Lower-risk MDS

For patients with lower-risk IPSS scores, the goal is to ameliorate cytopenias, abrogate transfusion dependence, improve quality of life and prevent complications of blood transfusions.

- Hematopoietic growth factors (HGFs) including erythroid stimulating agents (ESAs) used in combination with granulocyte colony stimulating agents may be effective in some select patients when used in supraphysiologic doses. HGFs are associated with improved survival in patients with lower transfusion needs and in those who respond to therapy.
- Lenalidomide is the only disease-modifying therapy available in Canada for del 5q MDS. Lenalidomide is an immunomodulatory drug related to thalidomide, but with greatly reduced clinical symptoms. MDS patients with deletion 5q (del 5q) constitute roughly 10% of all MDS. In this patient group, lenalidomide can achieve red blood cell independence in 67% of MDS patients who are chronically red cell transfusion dependent and complete cytogenetic remissions in 45%.
- Iron chelators including the parenteral drug deferoxamine and the oral iron chelator deferasirox are indicated in patients who are chronically transfusion dependent and have serum ferritins that exceed 1000 ug/l or have received more than 20 to 25 units of blood. Iron chelation is most appropriate for patients

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with lower risk MDS scores or those destined for an allogeneic stem cell transplant. Patients are instructed to record the dates of their transfusions and the numbers of units received in order to appropriately administer iron chelators as soon as indicated.

- Immunosuppressive agents including cyclosporine and antithymocyte globulin may be used in younger patients with MDS.
- New targeted 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 drugs such as 5-Azacitidine, decitabine and the histone deacetylase inhibitors such as vorinostat and valproic acid.
- Major phenotype matched red blood cell transfusions should be offered at symptomatic thresholds individualized for the patient. Routine prophylactic platelet transfusions in symptomatic patients should be avoided in order to minimize allo-immunization. Antifibrinolytics such as transexamic acid should be used instead to minimize mucosal bleeding.

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Higher-risk MDS

For patients with higher-risk MDS, the primary goals of treatment include preventing the development of leukemia, improved survival and quality of life.

- The only potential cure for MDS is an allogeneic stem cell transplant from a related donor. Very few elderly patients are candidates for this because of the lack of donors or precluding comorbidities. A younger patient would be referred for an allo-stem cell transplant if a donor were available. Selected older patients might also be candidates for reduced intensity "non-myelo-ablative" transplants if a donor was identified.
- Traditional higher-dose chemotherapy (as used for acute myeloid leukemia) is toxic in the elderly and remissions (if achieved) are rarely durable.
- The hypomethylating agents such as 5-Azacitidine and decitabine that target the epigenetic silencing of genes have been shown to delay the time to leukemia and death in higher-risk MDS patients and are the drugs of choice in the absence of transplant if available. Currently, neither drug is licensed in Canada, but both are available by the special access program.
- Newer drugs that target angiogenesis, abnormal cytokine signalling in the microenvironment and the malignant clone are also in clinical development.

Take home messages

- MDS is a relatively common malignant stem cell disorder in the elderly and presents with cytopenias with or without constitutional symptoms, infection or bleeding. It is likely under-diagnosed in the elderly.
- MDS is associated with increased morbidity and mortality compared with age-matched controls due to bleeding, infections, cardiac failure and leukemia.
- Diagnosis can only be made by bone marrow aspirates and biopsies with cytogenetics performed by experienced physicians.
- There are a variety of therapies available tailored for MDS risk groups and subtypes that may improve quality of life, eliminate transfusions and even change the natural history of the disease.
- Red blood cell transfusions should be offered in patients with symptomatic anemia, but the hemoglobin threshold should be individualized. Platelet transfusions should be minimized and offered for symptomatic clinically significant bleeding only. Instead, antifibrinolytic agents may be used for superficial (non-life-threatening) mucosal bleeding in appropriate patients.
- Any patient with unexplained cytopenias should be referred to a hematologist with expertise in treating MDS for diagnosis and therapy.

Did you know that the Odette Cancer Centre of Sunnybrook Hospital is a recognized "Centre of Excellence" for MDS care, therapy, clinical and basic science research?

Using informed consent, we register all patients in an MDS clinical database and bank bone marrow aspirate samples when diagnostic bone marrows are performed. Patients are asked to complete quality-of-life questionnaires several times per year at routine clinical visits. We welcome all referrals.

Referral information

We would be delighted to assess patients with unexplained cytopenia(s) or patients with a pre-existing diagnosis of MDS who may be interested in clinical trials or the optimization of MDS therapies.

Please contact **New Patient** bookings at the Odette Cancer Centre for referrals to MDS clinics (Wednesday and Friday afternoons) at phone number (416) 480-4205; fax (416) 480-6179. Attention Drs. Rena Buckstein (416-480-5847) or Richard Wells (416-480-5248).

Please attach a brief summary of important medical problems and medicines.

Please include the following labs if available:

- CBC and blood film
- LDH, reticulocyte count, bilirubin, creatinine
- Ferritin, vitamin B12, rbc folate, TSH, free T4
- Any prior bone marrow reports and cytogenetics (if performed)

If patient is red cell transfusion dependent, please ask patient to bring with them transfusion records (if kept) with respect to dates and number of units transfused, transfusion reactions or allo-antibodies.