An Update on Myelodysplastic Syndrome

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In myelodysplastic syndrome (MDS), genetic mutations in bone marrow stem cells result in production of defective blood cells. These defective cells fail to meet the intrinsic "quality control" standards of the bone marrow and are not released into the circulation, leading to anemia, leukopenia or thrombocytopenia. In some, but not all, patients with MDS, there also is a greatly increased risk of development of acute myelogenous leukemia. Until very recently, therapeutic options in MDS were extremely limited. This article reviews recent advances in risk-based classification of MDS, and describes new therapies that promise to revolutionize our approach to patients with this disorder.

Key words: myelodysplastic syndrome, bone marrow, anemia, acute myelogenous leukemia.

Introduction

Anemia is a common clinical problem in older adults. In many cases a cause, such as nutritional deficiency or bleeding, can be readily identifiable and easily treated. However, the remaining unresolved cases present an important diagnostic and therapeutic problem. Myelodysplastic syndrome accounts for a substantial proportion of these "difficult" cases. Here we present the nature of this disease, and how can it be managed in the elderly.

Epidemiology

The term myelodysplastic syndrome (MDS) encompasses a heterogeneous group of disorders characterised by clonal hematopoiesis, qualitative abnormalities of blood cell differentiation, reduction in blood cell counts despite normal or increased bone marrow cellularity, and propensity to transform into acute myelogenous leukemia. MDS incidence rises sharply with age; a U.K. study estimated the incidence of MDS to be 0.5 per 100,000 per year in the < 50 year age group, rising to 89 per 100,000 per year in the > 80 years group.[1] The number of cases of diagnosed MDS has increased steadily over the past 30 years,[2] and this trend can be expected to continue over the next few decades as the populations of industrialized countries continue to age.

Presentation, Diagnosis and Prognosis

MDS is a frequent long-term complication of cancer chemotherapy but also may arise de novo, and should be considered in any patient with chronic anemia. Patients with MDS most commonly present with symptoms of anemia, although frequent bacterial infections, especially of the skin, or a bleeding tendency may be present. Some typical myelodysplastic changes in peripheral blood morphology are shown in Figure 1. The anemia is typically macrocytic but may be dimorphic (showing two distinct populations of red blood cells). Often, thrombocytopenia and leukopenia accompany the anemia. Peripheral blood neutrophils show characteristic dysplastic changes, including lack of cytoplasmic granules and paucity of nuclear segmentation.

Although it may be suspected from peripheral blood findings, the diagnosis of MDS relies upon examination of the bone marrow. Classically, bone marrow reveals normal or increased cellularity despite the peripheral cytopenias. This phenomenon, known as ineffective hematopoiesis, is the hallmark of MDS and establishes the diagnosis in the presence of dysplastic morphological abnormalities in peripheral blood and bone marrow. Chronic myelomonocytic leukemia (CMML) is an outlier among myelodysplastic syndromes—in addition to dysplastic changes and hypercellular bone marrow, there is an excess of monocytes in both blood and marrow. Indeed, controversy exists as to whether this entity should be classified as a MDS or as a myeloproliferative disease.

There are three main classification systems for MDS. The French-American-British (FAB) classification[3] subdivides MDS into five categories on the basis of bone marrow and peripheral blood cytology: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEBt), and CMML. Although the FAB classification is very widely employed in clinical practice, it correlates poorly with prognosis. The World Health Organization (WHO) classification[4] of MDS is an extension of the FAB classification that includes cytogenetic data. Although this represents an

Table 1

Summary of Prognosis of Patients with MDS by IPSS* Categories

	Low	Intermediate-1	Intermediate-2	High
Median survival (years)	6	3.5	1	0.5
Evolution to acute myelogenous leukemia	Uncommon, ~20% at 10 years	~25% at 3.5 years	~50% at 3 years	Rapid, ~50% at 6 months

*IPSS: The International Prognostic Scoring System

improvement, its value in predicting prognosis remains to be validated prospectively. The International Prognostic Scoring System (IPSS)[5] incorporates the extent of peripheral cytopenias, bone marrow cytogenetics and percentage blasts in bone marrow. Using these data, a score is determined for each patient, permitting placement into one of four risk groups that predict for survival and evolution to acute myelogenous leukemia (AML). The prognostic implications of these four categories (low, intermediate-1, intermediate-2 and high) are summarized in Table 1.

The Biology of Myelodysplastic Syndrome

In MDS, intrinsic defects in developing blood cells are sensed by the cells "quality assurance" program, triggering the suicide of the defective cells by apoptosis. This elicits a cell-mediated immune response, which amplifies this destruction of developing blood cells in the bone marrow, resulting in the phenomenon of ineffective hematopoiesis. The identification of the intrinsic defects that underpin this process has been a research area of great interest.

Approximately 40–50% of cases of de novo MDS and 80% of t-MDS exhibit clonal cytogenetic abnormalities at the time of diagnosis.[6] Unbalanced abnormalities resulting in the loss or gain of genetic material are seen most frequently, although balanced translocations occur in a significant proportion of cases. Complex karyotypes, in which multiple independent abnormalities are present, are common, especially in t-MDS.[7,8] In 1–3% of cases, multiple distinct clones can be identified on the basis of chromosomal changes.[9]

Loss of all or part of chromosomes 5 or 7 represents by far the most common cytogenetic changes in MDS. The -5/del 5(q) genotype occurs in 30% of MDS cases. A subset of these comprise the "5q-syndrome", a variant of refractory anemia predominantly affecting women and characterized by normal or elevated platelet count and good prognosis.[10-12] Abnormalities of chromosome 5 also are frequently seen in t-MDS,[7,8] wherein they are associated with a poor prognosis. Loss of all or part of chromosome 7 is seen in 10% of MDS cases overall,[13] and in 50% of t-MDS cases.[7,8] In 80% of patients, these are interstitial deletions encompassing the segment 7q22-7q31, while the remainder have a more distal deletion, of 7q32-33.[14]

The high frequency of these abnormalities strongly implies that they are of singular importance in the pathogenesis of MDS, although the molecular basis for the roles of these deletions remains unclear. In general, loss of chromosomal material implies involvement of tumour suppressor genes. Chromosomes 5 and 7 contain many genes important for hematopoiesis. Several researchers are pursuing investigation of these genes as potential candidates in MDS. In addition to gross genomic changes that are evident cytogenetically, more subtle changes, such as point mutations in oncogenes and tumour suppressor genes, likely play a role in MDS pathogenesis as well. Identification of such lesions will provide the foundation for the development of new therapies for this disorder.

Treatment

The cornerstone of therapy for patients with low-risk MDS is supportive care, involving transfusion of erythrocytes and platelets, and surveillance and antibiotic therapy for infections complicating neutropenia. Although these patients have a relatively low risk of developing AML, chronic transfusion requirement frequently leads to iron overload with clinically important myocardial, hepatic and pancreatic dysfunction, so that morbidity in this group is high.[15-17] Although treatment with erythropoietin can reduce transfusion requirement in a small proportion of patients,[18] supplementation with other hematopoietic growth factors, including G-CSF, GM-CSF, IL3 and IL11, has yielded disappointing results, with little clinically important alleviation of cytopenias.[19]

Current therapy for intermediate- and high-risk MDS also is far from satisfactory. Because these disorders tend to evolve rapidly into AML, the mainstay of

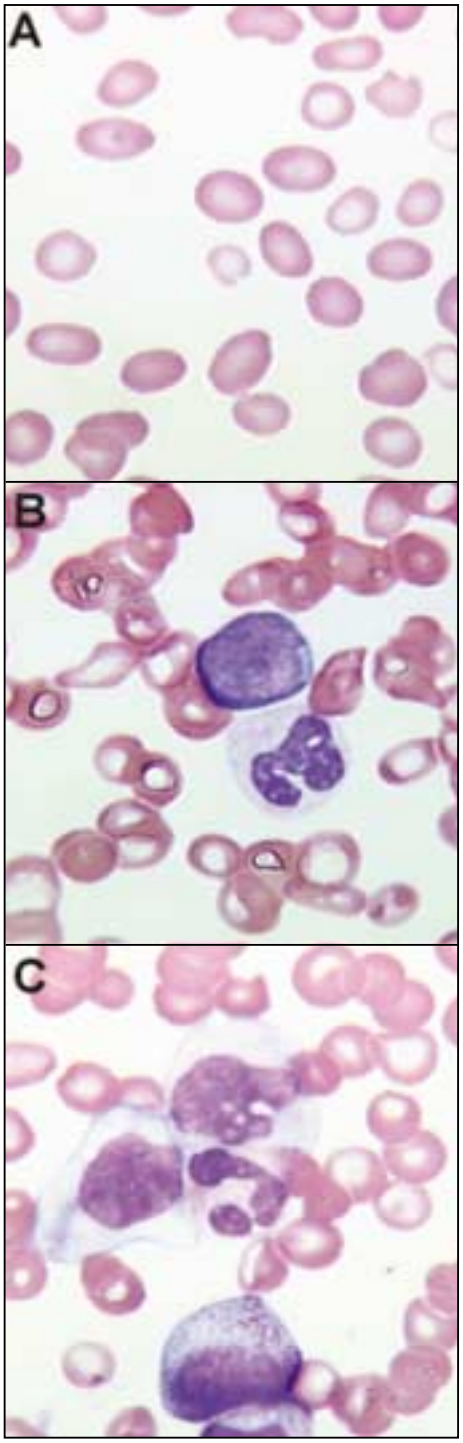

Figure 1: Some Abnormalities of Peripheral Blood Morphology Typical of MDS

A. Dimorphic erythrocytes. Note the populations of tiny, pale erythrocytes and larger, better hemoglobinized erythrocytes.

B. Hypogranular neutrophil and blast. The appearance of blasts (primitive cells) in the peripheral blood may herald the evolution of MDS into acute leukemia.

C. Chronic myelomonocytic leukemia. Two abnormal monocytes are seen straddling a hypogranular neutrophil.

treatment has been intensive chemotherapy. However, relative resistance to antileukemic chemotherapy characterizes MDS, probably due to a reduced pool of normal hematopoietic stem cells. When remission of disease is achieved, its duration is consistently short despite initial hematological recovery following treatment.[20-22] For this reason, several other approaches to MDS treatment have been proposed.

Differentiation therapy with a variety of agents, including 13-*cis* retinoic acid, vitamin D_3, dimethyl sulfoxide, hexamethylene bisacetamide and low doses of the cytotoxic agent cytosine arabinoside, has been proposed. However, in clinical studies most of these show only marginal or transient benefits.[23-25] Treatment with interferons α and γ has yielded similarly unpromising results.[25,26] Allogeneic bone marrow transplantation has proved to be successful in a subset of patients with MDS. The European Bone Marrow Transplant Registry reported disease-free survival rates of 32% in RAEB and 27% in RAEBt.[27] Fewer studies have been published for RA, RARS and CMML, and it is unclear if bone marrow transplantation is indicated for patients with these diagnoses. Despite significant advances in transplant technology and supportive care, this modality of treatment remains highly toxic and is generally not considered safe for patients older than 60 years.

The Cutting Edge—Promising New Treatments for MDS

In the past two years new MDS treatments have been described that promise to revolutionize the management of this disorder. These new therapies will likely be available soon for routine use in Canada.

The closely related agents 5-azacytidine (5-aza) and 5 aza-2'-deoxycytidine (decitabine) are the best studied of the new agents. These drugs act by inhibiting the enzyme DNA methyltransferase (DMT), an important modifier of gene expression. DNA methylation is normally used by the cell to "switch off" genes that should not be expressed in a particular tissue. Inappropriate gene methylation has been documented in MDS and in a variety of human cancers. For example, hypermethylation of the cell-cycle inhibitory kinase p15INK4b is common in MDS patients in whom the bone marrow blast count is greater than 10%.[28] By reversing inappropriate DNA methylation, 5-aza and decitabine can reprogram MDS stem cells to differentiate more effectively and thus to contribute to blood cell production. This has been shown in several clinical trials to result in significant clinical improvement in MDS patients, including improved blood counts, reduced transfusion requirement, improved quality of life and reduced risk of transition to acute leukemia.[29-32]

Another promising approach to MDS treatment is intensive immunosuppression with antithymocyte globulin (ATG). This modality is predicated on the notion that T-cell-mediated destruction of bone marrow cells is an important contributor to ineffective hematopoiesis in MDS. Early phase clinical studies showed a 20–30% rate of response to ATG in MDS, but because of the high cost and unfavourable safety profile of ATG, it has not been enthusiastically adopted. However, a recent trial has shown that MDS patients who express the HLA-DR15 antigen have a significantly higher chance of responding to ATG therapy (~50%, compared to < 20% of antigen-negative patients).[33] It is therefore now possible to select patients who have a high probability of response and in whom the risks of ATG therapy may be worth taking.

A Management Approach to the Patient with MDS

The diagnosis of MDS must be established by bone marrow examination, and the IPSS risk category determined. It is helpful to measure baseline erythropoietin levels, as well as serum ferritin and transferrin saturation to establish an estimate of iron loading. For a patient with erythropoietin < 200 U / L, a trial of erythropoietin therapy is worthwhile at 40,000 U per week for 12 weeks. The possibility of allogeneic bone marrow transplantation should be considered for patients younger than 60 years. If transfusions are required, the patient's iron load should be monitored and liver enzymes, glucose tolerance and myocardial function should be assessed periodically. Significant iron overload can be treated by iron chelation with deferrioxamine. Referral should be made to a hematologist for consideration of treatment with a DMT inhibitor or ATG. ◆

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