Myelodysplastic syndromes

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders clinically characterised by peripheral cytopenia, followed by a progressive impairment of myelodysplastic stem cells. The natural history of MDS, ranging from indolent conditions spanning years to forms rapidly progressing to leukaemia, are reviewed by **Dr Nabil Aly** as are methods of diagnosis and available therapies.

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Myelodysplastic syndromes (MDS) are a group of closely related clonal haematopoietic disorders. It is used to describe a condition characterised by refractory cytopenias in patients whose bone marrow reveals dysplastic changes in at least two of the three haematopoietic cell lines. All share a few characteristics that include a cellular marrow with impaired morphology and maturation, (dysmyelopoiesis) and peripheral blood cytopenias resulting from ineffective blood cell production. The term 'dysmyelopoietic' or 'myelodysplastic syndrome' refers to a qualitative and quantitative abnormality of haematopoietic cells that sometimes progresses to acute leukaemia. However, dyshaematopoietic states with a well-understood reversible basis, such as B12 or folate deficiency, are specifically excluded.

Age-related haematopoietic changes

Normally, the process of haematopoiesis constitutes the process of producing diverse, differentiated blood cell types in a manner related to physiological requirement. At any given time, 90 per cent of stem cells are quiescent and 10 per cent are cyclic. Modulation of haematopoiesis becomes disordered, which means impairment of older people's ability to respond appropriately to the physiological demand for blood cell replacement. The later is usually triggered by stimuli such as blood loss or cytoreductive chemotherapy. In addition, various age-related events, such as genomic mutations secondary to oxidative stress and impaired regulation of cytokine production, may contribute to or cause the emergence of abnormal clones of haematopoietic cells[1]. Therefore, normal haematopoiesis is disrupted, and the haematopoietic system is populated with cells that are quantitatively and functionally deficient and are also subject to leukaemic transformation. These defects in the production and maturation of the various differentiated blood cells are referred to as MDS, which are so tightly associated with ageing[1]. These syndromes can lead to anaemia, neutropenia, thrombocytopenia and the development of acute nonlymphoblastic leukaemia. In addition, the increased interleukin-6 production frequently found in the older individuals may participate in promoting the survival and proliferation of malignant myeloma and in inducing resistance by myeloma cells to therapies that act through apoptosis (programmed cell death)[2].

Pathophysiology

In MDS, there is a defect at the level of the haematopoietic stem cell where the abnormal clone has a competitive growth advantage and, over time, occupies a significant fraction of active stem cell compartment. A clonal mutation predominates over bone marrow, suppressing healthy stem cells. An age-associated decrease in the expression of

interleukin-2 may contribute to impaired cellular immunity[2]. In early stages of MDS, the main cause of cytopenias is increased apoptosis. As the disease progresses and converts into leukaemia, a rare gene mutation may occur and a proliferation of leukaemic cells overwhelms the healthy marrow. There is some evidence favouring the role of cytokines in MDS[1,2]. The fact that stromal cells in MDS marrows are also apoptotic, implies the cause is in the local environment and not genetic. Also, TNF-alpha is present in increased amounts in the marrows of about 75 per cent of MDS patients and IL1-beta is another possible candidate cytokine. Mature CD3,4 cells(T cell with CD3/CD4 receptor that can recognise certain surface antigens) also may undergo apoptosis and this would explain the paradox of increased marrow cellularity and proliferative rate with simultaneous pancytopenia and apotosis[1,2].

Aetiology

MDS can be divided into two categories: primary and secondary. Primary MDS develops *de novo* and about 40–60 per cent of these patients have cytogenetic abnormalities at diagnosis, whereas more than 80 per cent of patients with secondary MDS have abnormal karyotypes of bone marrow cells[7]. Secondary MDS can arise as a result of prior chemotherapy, chemoradiotherapy for other malignancies or as a result of exposure to a variety of marrow toxins such as alkylating agents. Other leukaemogenic chemicals such as benzene have been implicated while insecticides, weed killers and fungicides are possible causes of MDS and secondary leukaemia.

Primary, or idiopathic, MDS are the most common, since approximately 60–70 per cent of patients do not have an obvious exposure or cause for MDS. Patients with more aggressive disease and those in leukaemic transformation tend to have more complex abnormal karyotypes. Structural and numeric chromosomal abnormalities are seen in MDS, and deletions are extremely common. The 5q- abnormality is most commonly observed; monosomy 7 is seen most often in patients with secondary MDS. Chromosomal abnormalities in primary and secondary MDS can involve chromosomes 5, 7, 8, 11, 12, and 20[7,8].

Clinical features

Patients with MDS may have no symptoms, so it is abnormal blood counts noted on routine examination that lead to the diagnosis. However, most patients present with the signs and symptoms of bone marrow failure such as anaemia, neutropenia and thrombocytopenia, causing fatigue, infection and bleeding, respectively. Pallor of the skin and mucosal membranes or evidence of fatigue, tachycardia or congestive heart failure may be manifestations of severe anaemia. Petechiae, ecchymoses, epistaxis and gum bleeding are common manifestations of low platelet count. If underlying dysplastic changes were missed initially, thrombocytopenia as the presenting symptom may be mistaken for immune thrombocytopenia. Poor platelet function is another cause of increased risk of haemorrhage. Fever, cough, dysuria or shock may be manifestations of serious bacterial or fungal infections associated with neutropenia. A poor granulocytic function of the existing neutrophils also is attributed to increased risk of infection.

Diagnoses and investigations

Careful history, particularly looking for exposure, and physical assessment are important for the diagnosis. However, some investigations are required to confirm and classify MDS. Bone marrow cellularity may be normal or increased, and dysmorphology may be present in any or all three cell lineages[9]. Erythrocytes are most commonly affected; anaemia occurs due to ineffective erythropoiesis as demonstrated by low reticulocyte counts despite normal numbers of erythroid progenitor cells[9].

Peripheral blood and marrow studies

Peripheral blood counts may reflect a single cytopenia (anaemia, thrombocytopenia or neutropenia) in the early phase or bicytopenia (two deficient cell lines) and pancytopenia (three deficient cell lines) in later stages. Anaemia may vary in degree from mild to severe. It is usually macrocytic (mean cell volume of >100 fL) with oval-shaped red cells (macro-ovalocytes) or dimorphic (two or more populations) consisting of a normal or a hypochromic microcytic population coexisting with the macrocytes[10]. Punctate basophilia may be observed in red cells. Morphologic abnormalities in the granulocytes often are observed, which can include bilobed or unsegmented nuclei (pseudoˆPelger-Huet abnormality) or hypersegmentation on the nuclei (six to seven lobes) similar to megaloblastic diseases. In most cases, bone marrow changes would include hypercellularity with trilineage

Table 1. The International Prognostic Scoring System (IPSS) for staging

Prognostic Variable	0 Points	0.5 Points	1.0 Point	1.5 Points	2.0 Points
Bone marrow blasts (%)	<5	5-10	...	11-20	21-30
Karyotype*	Good	Intermediate	Poor	...	...
Cytopenias	0/1	2/3	...	...	...

*Good: no abnormality (46, XX or XY), -Y, del (5q), del (20q)
Intermediate: other abnormalities, such as trisomy 8 (+8)
Poor: complex (3 abnormalities or chromosome 7 abnormality; ie, 7q- or -7)

(erythroid or red cell lineage, platelet production cell or megakaryocyte lineage, myeloid cell line) dysplastic changes. A small number of patients may have hypocellular marrow, which often overlaps with aplastic anaemia, and increased marrow fibrosis may be confused with other myeloproliferative disorders. Dysplastic changes in red cell lineage (dyserythropoiesis) are characteristic. Dysthrombopoiesis in the platelet production cell lineage consists of micromegakaryocytes (dwarf forms) with poor nuclei lobulation and giant platelets budding off from their cytoplasm. The presence of dysplastic changes in the peripheral blood smear and trilineage dysplasia and hypercellular marrow in the absence of vitamin deficiency is diagnostic of MDS. The presence of typical chromosomal abnormalities supports the diagnosis and contributes to determining the prognosis.

Cytogenetic studies

Cytogenetic studies of the bone marrow cells indicate mutations into clonal cell lines, with abnormal chromosomes in 48–64 per cent, in different series[7]. Chromosomal abnormalities are clonal and include 5q-, monosomy 7 (-7) or 7q-, trisomy 8 (+8), and numerous other less frequent abnormalities. Multiple combinations may be present, which indicate a very poor prognosis. A single abnormality, except those involving chromosome 7, usually indicates good prognosis and survival[8]. The new technique using FISH (fluorescent in situ hybridisation) and colour-coded chromosomes enables observation of the intact cell without requiring mitosis.

Staging

Patients with MDS have heterogenous clinical manifestations and varying clinical outcome, so staging is necessary for estimating their prognosis and approaching therapy, depending on the severity and stage. The criteria for staging of MDS are called the International Prognostic Scoring System (IPSS) (*Table 1*). Four risk groups can then be distinguished, based on total point score[11]:

- good total score: 0 point;
- intermediate-1: total score 0.5–1.0 point;
- intermediate-2: total score 1.5–2.0 point;
- poor: total score 2.5 or above.

Complications

The clinical course of MDS are highly variable, and the median survival in most studies ranges from 20 to 36 months (median survival 22 months)[12]. MDS has the risk of complications associated with severe cytopenias, such as acute myeloid leukaemia (AML). Other complications include development of myelofibrosis that can accelerate decline in blood counts and increase transfusion requirements, and transformation to acute leukaemia accelerates the development of complications such as anaemia, bleeding and infections. Patients with splenomegaly may have complications related to spontaneous rupture and intra-abdominal exsanguination.

Management

General lines

The natural history of MDS, ranging from indolent conditions spanning years to forms rapidly progressing to leukaemia, complicates clinical decision-making regarding therapeutic modalities and timing of intervention[12]. The mainstay of therapy has been supportive care, including red blood cell and platelet transfusions for symptomatic anaemia, and thrombocytopenia and antibiotics for infection. MDS is generally an indolent disease affecting the older individuals. Therefore, any attempt at systemic treatment must cause very limited toxicity. Stratification according to the risk categories, using bone marrow examination and the IPSS scheme, is necessary to determine the therapeutic efficacy of various treatment regimens.

A younger patient with a more aggressive form of MDS probably warrants aggressive systemic treatment, while an older patient with an indolent form of the disease probably should receive only supportive care. The possibility of allogenic bone marrow transplantation should be considered for patients younger than 60 years[10]. However, since most patients are in the older age group, and only a few young MDS patients will have a matched donor, the use of bone marrow transplantation is limited.

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 desferrioxamine. Treatment with the enzyme DNA methyltransferase (DMT) inhibitor, a modifier of gene expression, should be considered. DNA methylation is normally used by the cell to 'switch off' genes that should not be expressed in a particular tissue, and inappropriate gene methylation has been documented in MDS as well as a variety of human cancers[10]. Antithymocyte globulin (ATG) intensive immunosuppression, is another promising approach to MDS treatment.

MDS often undergoes transformation into AML, and the leukaemias in these patients are generally less responsive to standard induction chemotherapy than those arising *de novo*. Therefore, although the morphology of AML is similar regardless of whether the disease develops *de novo* or after transformation from MDS, the biology of the disease is not. There is no major role for surgery and splenectomy for the cytopenia is dangerous and fraught with complications. In general, therapeutic modalities should be considered according to the age, general performance state and the prognostic scores of individual patients[13].

Chemotherapy and other agents

Chemotherapeutic options for MDS range from intensive cytotoxic therapy to low dose treatment modalities. The use of intensive chemotherapy has led to variable complete remission (CR) rates (13–51 per cent) with significant morbidity and mortality[14,15]. The best results have been achieved in younger patients and in those with more favourable karyotypes. Cytosine arabinoside has been the most widely studied therapeutic agent, particularly at low doses. Low dose cytosine arabinoside therapy for MDS has a very low CR rate (eight to 17 per cent), about 35 per cent overall response rate, and produces no improvement in long-term survival[1].

Corticosteroids and androgens have also been tried and, although some patients respond transiently, no benefit in long-term survival has been achieved[16]. Granulocyte-macrophage colony stimulating factor (GM-CSF) has been used in MDS with modest success. In many patients, the neutrophil count rises and remains elevated as long as the drug is continued. However, side effects — including flu-like syndrome, bone pain and hyperleukocytosis — may cause up to 25 per cent of patients to discontinue the treatment[17]. Granulocyte colony stimulating factor (G-CSF) has also been used and is better tolerated than GM-CSF. Growth factor therapy using G-CSF results in persistent improvement in neutrophil counts, improved granulocyte maturation and decreased red blood cell transfusion requirements in patients who were transfusion-dependent[18]. G-CSF therapy can increase the neutrophil count, with minimal effects on other cell lines and with no significant change in platelet count. Maintenance therapy for up to 16 months has been shown to remain effective, although counts return to baseline within two to four weeks of discontinuing treatment[17,18].

Interferon therapy, preferentially cytotoxic against leukaemia cell lines, has been used and haematologic improvement has been noted in 30–50 per cent of a small number of treated patients. However, suppression of normal myelopoiesis is a significant problem[10]. Anticytokine therapy, such as TNF-alpha, acts as a growth factor for $CD_{3,4+}$ progenitor cells belonging to the dysplastic clone, helping them to proliferate and take over the marrow[19]. As they mature into $CD_{3,4-}$ myeloid precursors, TNF-alpha induces them to undergo apoptosis, producing marrow hypocellularity and cytopenia. The combination of pentoxifylline, ciprofloxacin, and dexamethasone has anti-cytokine activity. Pentoxifylline interrupts the production of intracellular diacylglycerol, a secondary messenger produces in response to cytokine binding to cells; while ciprofloxacin decreases the metabolic clearance of pentoxifylline and dexamethasone inhibits the translation of cytokine mRNA into protein[20]. About 42 per cent of MDS patients respond to this treatment, although it may take several months before haematologic and/or cytogenetic improvement occurs. However, there are no complete responses, because the underlying stem cell defect is not addressed.

Bone marrow transplantation

Currently, allogeneic bone marrow transplantation using an HLA-matched sibling donor is the only treatment proven to achieve long-term disease-free survival (DFS) in MDS patients. In one study, the DFS, relapse and nonrelapse four-year mortality were 41 per cent, 28 per cent and 43 per cent, respectively, with patients younger than 40 years of age and those with <5 per cent marrow blast counts had a better prognosis (DFS in 62 per cent)[21]. Patients with secondary MDS had a 25 per cent DFS in the same study. Another study has evaluated myeloablative therapy followed by allogeneic transplantation using unrelated donors and showed a two-year DFS of 38 per cent, with relapse and nonrelapse mortality of 28 per cent and 48 per cent, respectively[22]. In both studies, younger patients with fewer than five per cent blasts in the bone marrow had the best prognosis. Karyotype affects the prognosis for this procedure and patients with an abnormality of chromosome 7 and/or complex abnormalities are three times more likely to fail[23].

Bone marrow transplantation with a matched allogenic (histocompatible) or syngeneic (identical twin) donor is sometimes used in patients with poor prognosis or late-stage MDS who are aged 55 years or younger and have an available donor. For patients who fail bone marrow transplant, donor leukocyte infusions have been suggested, but there are minimal data in myelodysplasia. Stem cell transplantation for MDS is characterised by high transplant-related mortality, especially in older patients and those with more advanced disease[24]. Outcome after peripheral blood stem cell transplantation may be superior to earlier results with bone marrow transplantation. However, although outcomes for all stages of primary MDS were improved, that for therapy-related MDS was associated with a high relapse rate (89 per cent)[24].

Transfusion therapy and erythropoietin

MDS patients with moderate-to-severe anaemia may require red blood cell replacement. Transfusing packed red cells for severe or symptomatic anaemia benefits the patient temporarily, only for the lifespan of the transfused red cells, which is about two to four weeks. Platelet transfusion is beneficial to stop active bleeding in thrombocytopenic patients, but the lifespan for transfused platelets is only three to seven days. Long-term measures to prevent skin and mucosal bleeding may be achieved by using oral antithrombolytic agents, such as aminocaproic acid. Life-threatening infections, especially fungal aetiologies, may require granulocytes transfusions together with antifungal agents.

Patient 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 desferrioxamine. The development of transfusion dependency and/or secondary iron overload significantly worsens the survival of patients with MDS[12]. In MDS, more long-term therapeutic approaches aimed at reducing transfusion needs, preventing iron overload and stimulating patient's bone marrow production of mature blood cells should be considered[12]. Erythropoietin (EPO) therapy may be warranted in some patients. It is helpful to measure baseline erythropoietin levels, as well as serum ferritin and transferrin saturation to establish an estimate of iron

Table 2. Prognostic scoring system in MDS based on IPSS scheme

Risk category of IPSS	Median survival (yr)	AML evolution (yr)*
Good	5.7	9.4
Intermediate-1	3.5	3.3
Intermediate-2	1.2	1.1
Poor	0.4	0.2

* time until 25 per cent of patients in the risk group develop AML

loading. For a patient with EPO < 200U/L, a trial of EPO therapy is worthwhile at 40,000U per week for 12 weeks[10]. Generally, the response rate is about 50 per cent and patients with low endogenous EPO levels probably will respond better. It is the least effective therapy in those with sideroblastic anaemia and those who have RBC (red blood cell) transfusion requirement. The combination of EPO and G-CSF has synergism over either agent used alone with approximately 40 per cent of patients achieve useful increase in haemoglobin, and a few become transfusion-independent[25].

Choice of treatment

The cornerstone of therapy for patients with low-risk MDS is supportive care, involving transfusion, surveillance and antibiotic therapy for infections complicating neutropenia. Chronic transfusion frequently leads to iron overload with clinically important myocardial, hepatic and pancreatic dysfunction in these patients, so that morbidity in this group is high. EPO therapy may reduce transfusion requirement in a small proportion of patients. However, supplementation with other haematopoietic growth factors — including G-CSF, GM-CSF, IL3 and IL11 — has yielded disappointing results, with little clinically important alleviation of cytopenias[9]. For the intermediate- and high-risk groups who tend to evolve rapidly into AML, the mainstay of treatment has been intensive chemotherapy. However, relative resistance to anti-leukaemic chemotherapy characterises MDS, probably due to a reduced pool of normal haematopoietic stem cells[10]. In younger patients, allogenic bone marrow transplantation, using either a matched sibling or unrelated donor, is the only available treatment that has resulted in long-term disease-free survival[9,10]. Patients with secondary MDS, and those who are in transformation to overt leukaemia, are more resistant to therapy and have a worse prognosis.

Prognosis

The disease course is variable, with some cases behaving as an indolent disease and others behaving aggressively with a very short clinical course that converts into an acute form of leukaemia. Several studies have employed multivariate analysis to distinguish prognostic subgroups of MDS. The IPSS was devised in 1997 using results from 816 previously studied patients[11,26]. The IPSS is based on bone marrow blast percentage scored into four ranges, number of peripheral cytopenias, and karyotype categorised in three groups[12]. Despite some discrepancies, the IPSS has been extensively validated in independent patient populations, and has become a benchmark for clinical trials and clinical decision-making[12]. The total IPSS score is calculated, and the patient is staged into four sub-groups (*Table 2)*:

- low (0);
- intermediate 1 – (0.5-1);
- intermediate 2 – (1.5-2); and
- high (greater than or equal to 2.5).

FAB (French-American-British Cooperative Group) subclass and advanced age also influence prognosis.

Histology, using immunohistochemical techniques, may have a role as prognostic factor[27]. Thus, the presence of abnormally localised immature precursors in the intertrabecular region of marrow may signify a poor prognosis with increased risk of transformation to acute leukaemia. The presence of N-ras mutations, as detected by PCR (polymerase chain reaction), is associated with shortened survival and increased risk of leukaemic transformation. It occurs in nine to 10 per cent of cases, and does not appear to correlate with cytologic subtype[28]. Older MDS patients with trilineage dysplasia and greater than 30 per cent myeloblasts that progress to acute leukaemia often are considered to have a poor prognosis because their response rate to chemotherapy is lower than *de novo* acute myeloid leukaemia patients. While MDS with isolated erythroid (red cell line) lineage dysplasia identifies a subset of truly low-risk patients, whose survival is significantly affected by demographic variables rather than by disease features[12].

Key points

- MDS most commonly occur in older patients and frequently pursue an indolent disease.
- MDS are characterised by pancytopenia with a hypercellular bone marrow due to ineffective haematopoiesis which causes bone marrow failure.
- Anaemia is probably the hallmark of MDS in older people.
- Primary form should be distinguished from secondary MDS associated with antineoplastic or immunosuppressive therapy, or exposure to toxic compounds.
- The mainstay of therapy is supportive care, including red blood cell and platelet transfusions for symptomatic anaemia, and thrombocytopenia and antibiotics for infection.

Conclusion

MDS is characterised by dysplastic changes in at least two of the three blood cell lineages in the bone marrow. MDS most commonly occurs in older patients and frequently pursues an indolent disease. Dysregulation of the expression of some cytokines may be a mechanism contributing to age-related impairment of the haematopoietic response, the genesis and therapeutic resistance of specific malignancies. The combined cytological and histological diagnosis of bone marrow and peripheral blood is a reliable tool for the initial diagnosis of MDS. In addition, cytogenetic and molecular analysis should be performed.

Presently, the risk of leukaemic transformation is evaluated using the IPSS for MDS, which is the sum of the scores of bone marrow blasts, karyotypes and cytopenia. Generally, the most appropriate treatment is supportive. For younger patients, allogeneic bone marrow transplantation or allogeneic stem-cell transplantation should be considered. Patients with secondary MDS or those in transformation to overt leukaemia are more resistant to therapy and have unfavourable prognosis.

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