Refractory Anemia and the Myelodysplastic Syndromes

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Refractory anemia is a component of each of the myelodysplastic syndromes (MDSs). MDSs are acquired pluripotent stem cell disorders leading to one or more peripheral blood cytopenias with dysplasia in the peripheral blood and bone marrow. MDS and aplastic anemia are sometimes grouped as bone marrow failure disorders because patients present with similar peripheral blood pictures. The bone marrow in MDS is generally hypercellular, due to ineffective hematopoiesis, in contrast to the hypocellular bone marrow of aplastic anemia. MDS is more common in the elderly, differing from aplastic anemia that affects all ages. The characteristics of each of the subgroups of the MDS using the World Health Organization (WHO) classification are described. Cytogenetic analysis provides a useful part of disease diagnosis in this new classification system. There is no successful treatment for MDS other than hematopoietic stem cell transplantation which is usually recommended for patients under age 50. A prognostic scoring system has been developed to help predict the severity of disease and guide treatment. Approximately 10% to 40% of MDS cases terminate in acute leukemia. Current treatment consists mostly of supportive measures; however several new therapies are being explored.

ABBREVIATIONS: AA = aplastic anemia; AML = acute myelogenous leukemia; CMML = chronic myelomonocytic leukemia; FAB = French-American-British; MDS = myelodysplastic syndrome; RA = refractory anemia.

INDEX TERMS: myelodysplastic syndrome; refractory syndrome.

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Refractory anemia (RA) is part of the group of disorders known as the myelodysplastic syndromes (MDSs). MDSs are neoplastic clonal stem cell disorders characterized by one or more cytopenias in the peripheral blood and dysplasia in both peripheral blood and bone marrow. The bone marrow is typically hypercellular and the cytopenias are a result of ineffective hematopoiesis. About one third of MDS cases progress into a condition similar to acute myelogenous leukemia (AML).[1] The tendency for this group of diseases to terminate in leukemia led to the term preleukemia, which was used until 1976 when the French-American-British (FAB) classification proposed the term "dysmyelopoietic syndromes", which included refractory anemia with excess blasts (RAEB) and chronic myelomonocytic leukemia (CMML).[2] The classification was later expanded and refined using the term "myelodysplastic syndromes".[3] Preleukemia is no longer considered an acceptable term, as this avoids giving the patient the unnecessary psychological trauma of a leukemia diagnosis.

Refractory (non-responsive) anemia is a component of each MDS category. MDS patients typically present with unexplained anemia without an increase in reticulocyte count. Anemia was the major presenting finding in 85% of a recent study of 117 MDS patients.[4] The anemia may be accompanied by leukopenia and/or thrombocytopenia depending upon the subtype. Isolated cases of refractory thrombocytopenia and/or neutropenia may be found without coexisting anemia, but these are very rare.

Table 1. World Health Organization (WHO) classification and criteria for the myelodysplastic syndromes

Disease	Peripheral blood findings	Bone marrow findings
RA	Anemia None or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
RARS	Anemia No blasts	Erythroid dysplasia only ≥15% ringed sideroblasts <5% blasts
RCMD	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in two or more myeloid cell lines <5% blasts, no Auer rods <15% ringed sideroblasts
RCMD-RS	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in two or more myeloid cell lines <5% blasts, no Auer rods ≥15% ringed sideroblasts
RAEB-1	Cytopenias <5% blasts No Auer rods <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
RAEB-2	Cytopenias 5% to 19% blasts Auer rods ± <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods ±
5q- syndrome	Anemia <5% blasts Platelets normal or increased Isolated del(5q)	Normal to increased megakaryocytes with hypolobulated nuclei <5% blasts, no Auer rods
MDS-U	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes <5% blasts, no Auer rods

RA = refractory anemia; RARS = refractory anemia with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia, RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB = refractory anemia with excess blasts; MDS-U = myelodysplastic syndrome, unclassified

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MDS and aplastic anemia (AA) are sometimes grouped as 'bone marrow failure conditions' because patients present with similar peripheral blood pictures: one or more cytopenias. However, there are distinct differences in epidemiology, bone marrow histopathology, and response to therapy.[5] The similarities and differences will be highlighted throughout this review.

CLASSIFICATION

The heterogeneity of the MDSs makes them difficult to classify. The FAB classification has been the accepted standard for classification of the MDS for more than two decades.[2,3] This classification system divides them into the five subtypes listed below:

1. refractory anemia (RA),
2. refractory anemia with ringed sideroblasts (RARS).
3. refractory anemia with excess blasts (RAEB),
4. chronic myelomonocytic leukemia (CMML), and
5. refractory anemia with excess blasts in transformation (RAEB-t).

The FAB groupings are based on morphological features, the number of blasts, and degree of dyspoiesis in the peripheral blood and bone marrow. Due to the heterogeneity of this group of disorders, it is difficult to classify some cases into a particular subgroup, using morphological criteria alone. There is also some overlap among the groups. The need to classify patients with MDS into more homogenous subgroups with similar clinical, biologic, and prognostic features, led to the proposal of the World Health Organization (WHO) classification system in 1997 (Table 1).[6] This system, developed by a group of American and European pathologists, hematologists, and oncologists, incorporates morphology, immunophenotype, genetics, and clinical features into classification of all neoplastic diseases of the hematopoietic and lymphoid tissues. The MDS category was affected by several major changes with this new classification system. CMML was removed and placed in a new category of diseases, the myelodysplastic/myeloproliferative diseases, because it has features of both categories. Another significant change was to lower the number of blasts in the bone marrow necessary for a diagnosis of AML from 30% to 20%. This eliminated the category of RAEB-t because patients with between 20% and 30% blasts tend to have the same prognosis as patients with >30% blasts. In addition, two new categories were added to the MDSs: refractory cytopenia with multilineage dysplasia (RCMD) and 5q- syndrome.

The new WHO classification has been validated by retrospectively applying it to approximately 1600 patients in a previous registry of MDS patients.[1] It has been suggested that the new grouping be used for upcoming clinical trials. Therefore, this review will summarize the subgroups of the MDSs using the new WHO classification. The various categories will be discussed in greater detail later in the article.

PATHOPHYSIOLOGY

The MDSs are neoplastic clonal disorders with the abnormal clone derived from an abnormal pluripotent stem cell. Chromosomal abnormalities are present in over 50% of patients at diagnosis and the number of chromosomal abnormalities correlates with the risk of progression to AML. Although the primary defect may be intrinsic genetic damage to a hematopoietic stem cell, other factors, such as interactions of this damaged cell with other cells, cytokines, or other signaling substances in the microenvironment, are involved. The ineffective hematopoiesis leading to peripheral blood cytopenias is the result of a complex interaction between hematopoietic progenitor cells and the microenvironment. The result is premature apoptosis (programmed cell death) of progenitors and failure of stem cells to mature and differentiate. The abnormal clone of cells also displays impaired responsiveness to cytokines and other growth factors. Both the microenvironment and the plasma of patients with MDS produce increased amounts of inflammatory cytokines, such as tumor necrosis factor-a (TNF-α) and interleukin-1β (IL-1β). These cytokines promote apoptosis of long-term initiating cells as well as of primitive and committed progenitors.[4] Angiogenic factors, such as vascular endothelial growth factor (VEGF), and mutations in oncogenes such as Ras, p53, platelet derived growth factor (PDGF), and CSF-1 receptor may also contribute to the development or progression of MDS and are being investigated as possible targets for MDS therapies.[4,7]

The major difference in pathophysiology of aplastic anemia and the refractory anemia of MDS is the hypocellular bone marrow in AA and the hypercellular marrow in MDS. The hypocellular marrow in AA is due to a critical deficiency of hematopoietic progenitor cells. In most cases these stem cells have been destroyed by autoreactive cytotoxic T-lymphocytes triggered by various medications, exposure to chemicals, or many unknown factors.[8] In the MDSs the hypercellular marrow with peripheral blood cytopenia is not due to lack of hematopoietic precursors, but other factors as discussed above.

EPIDEMIOLOGY

The MDSs are one of the most common hematological malignancies affecting adults. The incidence has been estimated

as 3.5/100,000 to 12.6/100,000 per year in the United States.[4] This range is wide due to the lack of a national registry for this disease; therefore incidence is based on estimation. These disorders are much more common in the elderly with the median age at diagnosis being between 60 and 80.[7] The risk of MDSs increases sharply with age. In contrast to the MDS, AA does not preferentially affect any age group and does not increase with age. The perceived recent increase in the MDS may be due to a growing awareness, better diagnostic techniques, and an aging population.[9] As the population of the industrialized world ages, along with the other factors mentioned above, the incidence of MDS is expected to rise dramatically over the next few decades.[4]

MDS is rare in children with the incidence estimated to be about the same as AML in children, about 15% of total cases of childhood leukemia. The median age of children at diagnosis is six years.

Although most cases of MDS are primary, it can be secondary to chemotherapy and/or radiotherapy for other malignant diseases. These cases are usually referred to as therapy-related MDS (t-MDS). It was first observed following treatment for Hodgkin's disease and has since been documented following treatment for cancers of the breast, lung, ovary, and gastrointestinal tract, as well as lymphoma, multiple myeloma, polycythemia vera, and chronic and acute lym-

Table 2. Summary of morphologic abnormalities common in MDS

PERIPHERAL BLOOD

Erythrocytes	Leukocytes	Platelets
Macrocytes	Agranular neutrophils	Giant platelets
Oval macrocytes	Hypogranular neutrophils	Hypogranular platelets
Anisocytosis	Persistent basophilic cytoplasm	Large fused granules
Poikilocytosis	Abnormal granulation	Micromegakaryocytes
Howell-Jolly bodies	Pseudo Pelger-Huet cells	
Basophilic stippling	Hypersegmentation	
Pappenheimer bodies	Ring-shaped nuclei	
Nucleated RBCs		
Dimorphism		
Schistocytes		
Acanthocytes		
Teardrop cells		

BONE MARROW

Erythroid precursors	Myeloid precursors	Megakaryocytes
Megaloblastoid forms	Abnormal staining primary granules	Micromegakaryocytes
Giant, multinucleated forms	Abnormal large primary granules	Large mononuclear forms
Nuclear fragmentation	Lack of primary granules	Agranular forms
Abnormal nuclear shape	Irregular cytoplasmic basophilia	Hypogranular forms
Nuclear budding	Lack of secondary granules	
Karryohexis	Nuclear abnormalities	
Irregular staining nuclei		
Ringed sideroblasts		
Defective hemoglobinization		
Cytoplasmic vacuoles		
Basophilic stippling		

phocytic leukemia. Development of t-MDS appears to be related to the duration, amount, and repetition of the therapy along with the age of the patient. The risk is greatest after exposure to alkylating agents. Chromosomal abnormalities occur in about 80% of t-MDS cases and tend to be more complex than those seen in primary MDS. Similar to primary MDS, about 30% of t-MDS cases evolve to acute leukemia. This category is included in the AML group with therapy-related AML in the WHO classification.[10]

CLINICAL FINDINGS

Fatigue and weakness due to anemia are the most frequent presenting symptoms of MDS patients. Symptoms related to neutropenia and thrombocytopenia, such as bacterial infection, easy bruising, epistaxis, and other types of bleeding are less likely to appear prior to diagnosis, but are common later in the disease process. Splenomegaly and/or hepatomegaly are rare upon initial presentation.

LABORATORY FINDINGS

Peripheral blood

The most striking MDS features are cytopenias and various forms of dysplastic cellular morphology in all cell lines. (Table 2). Anemia is the most common type of cytopenia, but neutropenia and/or thrombocytopenia may also occur. Approximately 39% of MDS cases have anemia alone, 27% have a decrease in erythrocytes and one other cell type, and 15% exhibit pancytopenia.[13] The higher the degree and number of cell lines decreased, the worse the prognosis.[10]

The erythrocytes are usually oval macrocytes similar to those seen in the megaloblastic anemias. Dimorphism, oval macrocytes, and microcytic hypochromic cells may be seen in some subgroups. Anemia varies but the hemoglobin level is usually less than 10 g/dL. Reticulocytes are usually inappropriately low for the degree of anemia. Anisocytosis, poikilocytosis, basophilic stippling, Howell-Jolly bodies, and nucleated erythrocytes are examples of dysplastic morphology commonly seen in MDS patients. See Table 2 for other examples.

Neutropenia may be accompanied by immature granulocytes, such as myelocytes and metamyelocytes, but rarely promyelocytes and blasts. Signs of dysplasia in the leukocyte cell line may be observed as abnormal granulation, such as agranular, hypogranular, or abnormally granulated neutrophils. Asynchrony in development may be seen with basophilic cytoplasm remaining in more mature cells. Pseudo Pelger-Huet (hyposegmented) cells may be seen as well as hypersegmentation of the nucleus or doughnut or ring-shaped nuclei. Neutrophils may exhibit functional abnormalities, such as defects in chemotaxis or bacteriocidal activity, in some cases.

The platelet count is variable and may be increased, normal, or decreased. Dysplasia may be observed in this cell line as giant platelets, hypogranular platelets, and/or platelets with abnormally large granules. Occasionally, small abnormal megakaryocytes (micromegakaryocytes) may be seen in the peripheral blood. Platelet functional abnormalities, such as abnormal aggregation and adhesion, may also be present in the MDSs.

Bone marrow

Bone marrow biopsy and smear examination are typically necessary to make the definitive diagnosis of MDS. The marrow is usually hypercellular or normocellular with erythroid hyperplasia. The percentage of blasts may be up to 20% using the new WHO classification. All three cell lines exhibit dysplastic features, sometimes referred to as "dyshematopoiesis". The most common dyshematopoietic feature in the bone marrow is asynchrony in cellular development similar to that seen in megaloblastic anemia. The nuclear development is lagging behind the cytoplasmic maturation. This type of maturation is often referred to as megaloblastoid development to distinguish it from true meglaoblastic development. Giant multinucleated erythroid precursors may be observed along with nuclear fragmentation, abnormal nuclear shape, nuclear budding, karryohexis, and irregular staining properties. None of these changes is responsive to vitamin B_{12} or folic acid therapy as in true megaloblastic anemia. Nucleated erythrocytes may show basophilic stippling, vacuoles, or defective hemoglobinization. Ringed sideroblasts, nucleated erythrocytes with mitochondrial iron deposits encircling the nucleus, are also common, reflecting abnormal erythrocyte metabolism.

Granulocyte production in the marrow is usually normal to increased. Evidence of abnormal granulocyte maturation (dysgranulopoiesis) is similar to the abnormalities seen in the cells in the peripheral blood. The granules of the promyelocytes and myelocytes sometimes exhibit abnormal staining, are larger than usual, or do not stain at all. Secondary granules are often absent in myelocytes and more mature cells leading to hypogranular neutrophils. Basophilia of cytoplasm is more frequent in precursor cells and nuclear abnormalities are similar to those described in the peripheral blood.

Abnormalities in the megakaryocyte cell line are exhibited as micromegakaryocytes, large mononuclear megakaryocytes, and megakaryocytes with other abnormal nuclear configu-

rations. The lack of granules or presence of giant abnormal granules in platelets is also common. Quantitatively, megakaryocytes vary from increased to normal, and to decreased.

Hypocellular bone marrow occurs in about 10% to 20% of cases of MDS. This makes differential diagnosis from AA more difficult. Differentiation is further complicated by the fact that treated AA may progress to MDS.[7] Dysplastic cellular features and cytogenetic analysis help to distinguish MDS and AA, but these may be inconclusive. Dysplasia in the erythroid cell line may be seen in AA; however, dysplasia in the myeloid and megakaryocytic cell lines is more representative of MDS. In addition, abnormal localization of immature myeloid precursors (ALIP) as seen on bone marrow biopsy is typical of MDS.[11] Normally, the most immature myeloid precursors are located in groups along the bone trabeculum. As the cells mature, they extend toward areas more central between bone trabeculae. ALIP refers to the abnormal location of these immature cells in the central marrow spaces and helps to distinguish MDS from other disorders.

Other laboratory findings

The serum iron is normal to increased and TIBC is normal to decreased. Iron stain on the bone marrow aspirate should be performed to identify the presence of ringed sideroblasts. Vitamin B_{12} and folic acid levels are normal to increased. This helps to differentiate MDS from true megaloblastic anemias. A battery of cytochemical and/or immunocytochemical tests should be performed to verify the origin of the blast cells present. Although most MDS blasts are of myeloid origin, the lymphoid cell line has rarely been involved.[12] Immunocytochemical testing may also be helpful to identify micromegakaryocytes (CD 41+, CD 61+), if present. Cytogenetic studies of the bone marrow have become an important part of the MDS diagnostic work-up. This information is also useful in estimating the prognosis and prescribing treatment. MDS patients with more complex chromosomal abnormalities have a worse prognosis and show increased incidence of progression to acute leukemia. Unlike AML, no specific abnormality has been associated with any subcategory, except for the 5q- syndrome which is discussed later in this article. The most common patterns in MDS patients involve structural or numeric abnormalities of chromosomes 5 and 7, and trisomy 8.

DESCRIPTION OF SUBGROUPS OF MDS (Table 1)

Refractory anemia (RA)

Anemia that is unresponsive to all conventional forms of therapy and a low reticulocyte count are the primary clinical findings. In RA, dysplastic morphology is restricted to the erythroid series. Approximately 5% to 10% of MDS cases fall into this category. RA is usually a diagnosis of exclusion: <1% blasts in peripheral blood and <5% blasts in bone marrow, $<1x10^9$/L monocytes in the peripheral blood, <15% ringed sideroblasts, and <10% of myeloid or megakaryocytic cells with dysplastic features. Erythrocytes are usually macrocytic, however, occasionally they appear microcytic or normocytic. Leukocytes and platelets are usually normal. The bone marrow shows erythroid hyperplasia and megaloblastoid erythropoiesis. This is a major difference from the hypoplastic marrow in AA. Only about 25% of RA patients have cytogenetic abnormalities. Median survival time is about five to six years and approximately 6% of patients in this category progress to AML[1].

Refractory anemia with ringed sideroblasts (RARS)

This category is very similar to RA with the exception of the presence of >15% ringed sideroblasts in the marrow. A sideroblast is a normoblast with five or more iron granules in an iron stain. If granules encircle at least one-third of the nucleus, the term "ringed sideroblast" is used. Approximately 10% to 15% of MDS cases are placed in this category. The peripheral blood and bone marrow morphology is similar to RA except for the increased presence of ringed sideroblasts. RARS may sometimes exhibit a dual population of erythrocytes, normochromic and hypochromic. About 10% of RARS patients have cytogenetic abnormalities and only about 1% to 2% progress into AML. Median survival time is six years.[1]

Refractory cytopenia with multilineage dysplasia (RCMD)

This is a category included in the new WHO classification system, but not in the former FAB classification. RCMD was created for cases of MDS with less than 5% blasts that have significant dysplasia involving granulocytic and megakaryocytic cell lines. Recent studies have shown that these cases are more likely to end in death due to bone marrow failure or to progress to acute leukemia than other cases that do not have these distinct features. The new RCMD category also helps to distinguish these cases from RA and RARS, which typically involve dysplasia in only the erythroid cell line. RCMD is similar to RA except it exhibits >10% dysplasia of myeloid and megakaryocytic cells. Approximately 24% of cases of MDS fall into this category and 11% progress into AML. Cytogenetic abnormalities are seen in up to 50% of RCMD patients and median survival is approximately three years.[1]

Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)

This is a subcategory of RCMD with similarities to RARS. The only difference from RCMD is that >15% sideroblasts are found in the bone marrow. RCMD-RS accounts for approximately 15% of MDS cases. Survival is similar to RCMD, but fewer patients progress to AML.

Refractory anemia with excess blasts (RAEB)

Patients who have greater than 1% blasts in the peripheral blood and greater than 5% blasts in the bone marrow are placed in this category. The erythrocytes are macrocytic or normocytic with reticulocytopenia. There is peripheral blood cytopenia in at least two cell lines and dysplastic signs in all three cell lines in both peripheral blood and bone marrow. The bone marrow is also hypercellular with varying amounts of granulocytic and erythroid hyperplasia. RAEB cases make up approximately 40% of MDS cases. Abnormal cytogenetic patterns are seen in 30% to 50% of RAEB cases. This category is further subdivided into RAEB-1 (5% to 9% bone marrow blasts and 1% to 5% peripheral blasts) and RAEB-2 (10% to 19% bone marrow blasts and 5% to 19% peripheral blasts). This new subdivision is due to prognostic differences that tend to correlate with number of blasts present. Median survival time for patients with RAEB-1 is 18 months and the rate of progression to AML is 25%. RAEB-2 patients have a median survival time of ten months and 33% progress into AML.[1]

5q- syndrome

Patients are placed in this category if the only cytogenetic abnormality present is del (5q) between bands 31 and 33 and they do not meet the criteria for RAEB. The other factors that distinguish this subtype are its good prognosis, median survival in the five to six year range, and unlikely progression to AML. It usually occurs in middle aged to older females with a macrocytic anemia, moderate leukopenia, and normal to elevated platelet count. The bone marrow contains less than 20% blasts and megakaryocyte hyperplasia with nuclear hypolobulation.

Unclassified MDS

The cases that do not meet criteria for other WHO subtypes are placed in this category. It includes patients with dysplastic features of the myeloid cell line alone or of both myeloid and megakaryocytic cell lines. As more information is gained about these cases further classification will take place.

MYELODYSPLASTIC—MYELOPROLIFERATIVE DISORDERS

This newly established WHO group includes disorders with features of both the MDS and the myeloproliferative disorders. It includes CMML, juvenile myelomonocytic leukemia, and atypical chronic myelogenous leukemia. Only CMML will be discussed in this review to illustrate a disorder showing features of both categories of diseases. CMML was originally categorized in the MDS under the FAB classification system, but was always described as quite different from the other subgroups.

Chronic myelomonocytic leukemia (CMML)

CMML characteristically exhibits a persistent monocytosis in the peripheral blood (>1x10^9/L) along with greater than 10% monocytes, <20% blasts, and granulocytic dysplasia in the bone marrow. Leukocytosis is common (46%) and leukopenia is rare (12%). About 38% of CMML cases exhibit prominent splenomegaly, which differentiates this disorder from the MDS. Absence of the BCR-ABL translocation distinguishes this disease from classic chronic myelocytic leukemia (CML). However, other cytogenetic abnormalities occur in approximately 20% to 40% of patients. The most common are monosomy 7 and trisomy 8. A relatively specific abnormality is deletion of 12, occurring in 15% of cases. The median survival time for CMML patients is 20 to 40 months and approximately 15% to 30% progress to AML.[1]

PROGNOSIS

There are no specific therapies for MDS. If not treated successfully by hematopoietic stem cell transplantation, these disorders are invariably fatal, except for the 5q- syndrome which has a good prognosis and low risk of transformation to AML. Approximately two-thirds of patients die within three to four years of diagnosis and those with more aggressive forms of MDS generally survive approximately one year.[7] The incidence of transformation to AML ranges from 10% to 40%. Although progression to AML is a primary concern, 20% to 40% or more of patients with MDS die of infections and/or hemorrhagic complications without progression to AML.

Several prognostic scoring systems have been developed for the MDS to help predict the severity of disease and insure appropriate treatment. The most widely accepted system in current use is the international prognostic scoring system (IPSS) as shown in Table 3. It was developed in 1997 at the International Myelodysplastic Syndrome Risk Analysis Workshop using data from seven large studies that had previously generated independent risk-based prognostic systems.[13] This

system is fairly simple to use, clearly distinguishes between groups with different outcomes, and has been validated by multiple groups.[14] The criteria upon which the IPSS is based are number of cytopenias, number (%) of blasts in the bone marrow, and karyotype. The lower the score, the better the prognosis. Although the IPSS was originally developed to predict prognosis and treatment intensity of MDS patients, it is also being used for prediction of survival and relapse probabilities after hematopoietic stem cell transplantation.[15]

TREATMENT

The selection of treatment for patients with MDS is influenced greatly by patient age and individual clinical and prognostic factors. Standard care consists of supportive measures such as transfusions to correct anemia, administration of hematopoietic growth factors, and cytokines to relieve neutropenia, and antibiotics to treat infections. Erythropoietin has been used with some success to treat anemia and reduce the frequency of transfusions. RARS appears to be resistant to erythropoietin treatment, and pyridoxine is sometimes useful.[1] The only treatment known to cure the MDSs is high-dose chemotherapy followed by stem cell transplantation. This is the treatment of choice for MDS patients under the age of 50, if a suitable donor is available. Overall disease free survival at three years with allogeneic stem cell transplantation ranges from approximately 35% to 60% depending upon IPSS score and other patient risk factors, especially age.[7] In some medical centers, transplantation is offered to patients up to 60 to 65-years-of-age, depending upon the IPSS score and disease progression.[15] An algorithm for MDS treatment developed by the National Comprehensive Cancer Network Myelodysplasia Panel is used to assist in the decision of whether or not to proceed with transplant.[15] In some cases conservative therapy may be preferable to transplant. The transplant procedure itself has a high mortality rate in patients over 50 and requires a suitable donor, therefore it is not an option for the vast majority of patients with MDS.

Because of the lack of suitable treatment options in MDS, several new therapies are being explored. Recent clinical trials with DNA methylation inhibitors that act as both biologic response modifiers and as cytotoxic agents, have produced significant clinical benefit.[7,12] Azacytidine and a related agent, decitabine, block DNA methylation which may lead to expression of previously silenced tumor suppressor genes and initiate transcription and differentiation. Thali-

Table 3. International prognostic scoring system (IPSS) for the myelodysplastic syndromes

Score value	Cytopenias	BM blasts (%)	Karyotype	Total score	Risk group	Median survival (yrs)
0	0-1	<5	Normal, -Y, del (5q) only del (20q) only	0	Low	5.7
0.5	2-3	5-10	Other abns	0.5-1.0	Int 1	3.5
1.0	—	—	Complex >2 abns chr 7 abns	1.5-2.0	Int 2	1.2
1.5	—	11-20	—	>2.5	High	0.4
2.0	—	21-30	—			

Cytopenias = hemoglobin <10g/dL, platelets <100x10^9/L, or neutrophils < 1.8x10^9/L in the peripheral blood
BM = bone marrow; abns = abnormalities; Int = Intermediate; yrs = years; chr = chromosome.

Adapted from: Greenberg P, Cox C, LeBeau MM, and others. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89(6):2079-88. Copyright American Society of Hematology, used with permission.

domide has been used on MDS patients and shown promising activity. Its use in MDS is based upon its potential antiangiogenic, anti-TNF-α, and immunosuppressive properties.[4,7] Farnesyltransferase inhibitors (FTI) regulate multiple proteins and/or cell-signaling pathways that have been implicated in MDS pathophysiology or progression, including Ras, p53, and other related cytokines. This regulation of multiple cancer-specific pathways has been proposed to explain the range of antiproliferative, antiangiogenic, and proapoptotic activity noted with these agents. These diverse actions combined with minimal impact on normal cells and the potential for oral delivery, make FTI attractive agents for testing in MDS. One of these FTIs, Zarnestra has been tried on MDS patients with promising early results. By regulating an assortment of tumor signaling cascades by inhibition of FTI, these agents may be exceptionally suited for broad activity in this heterogeneous group of disorders and certainly hold future promise.[4,7]

CONCLUSION

The myelodysplastic syndromes are stem cell disorders characterized by one or more peripheral blood cytopenias and prominent cellular maturation abnormalities. The bone marrow is usually hypercellular, indicating extensive ineffective hematopoiesis. Refractory anemia is the most common cytopenia but neutropenia and thrombocytopenia also occur. Erythrocytes are macrocytic or less frequently normocytic. Erythropoiesis in the bone marrow is abnormal with megaloblastoid features usually present. Neutrophils and platelets may also show dysplastic features. The WHO classification system divides the MDS into eight subgroups using morphology, immunophenotype, cytogenetics, and clinical features. A prognostic scoring system helps predict the severity of disease and direct treatment strategies. The MDS frequently terminate in acute leukemia. Treatment is mainly supportive unless the patient is a candidate for bone marrow transplant. Several promising new treatment approaches are being explored.

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