TABLE 130-6 INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)

	Score Value				
Prognostic Variable	**0**	**0.5**	**1**	**1.5**	**2**
Bone marrow blasts (%)	<5%	5–10%		11–20%	21–30%
Karyotype[a]	Good	Intermediate	Poor		
Cytopenia[b] (lineages affected)	0 or 1	2 or 3			
Risk Group Scores	**Score**				
Low	0				
Intermediate-1	0.5–1				
Intermediate-2	1.5–2				
High	≥2.5				

[a]Good, normal, –Y, del(5q), del (20q); poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate, all other abnormalities. [b]Cytopenias defined as hemoglobin <100 g/L, platelet count <100,000/μL, and absolute neutrophil count <1500/μL.

nuclei. Megaloblastic nuclei associated with defective hemoglobinization in the erythroid lineage are common. Prognosis strongly correlates with the proportion of marrow blasts. Cytogenetic analysis and fluorescent in situ hybridization can identify chromosomal abnormalities.

DIFFERENTIAL DIAGNOSIS

Deficiencies of vitamin B_{12} or folate should be excluded by appropriate blood tests; vitamin B_6 deficiency can be assessed by a therapeutic trial of pyridoxine if the bone marrow shows ringed sideroblasts. Marrow dysplasia can be observed in acute viral infections, drug reactions, or chemical toxicity but should be transient. More difficult are the distinctions between hypocellular MDS and aplasia or between refractory anemia with excess blasts and early acute leukemia. The WHO considers the presence of 20% blasts in the marrow as the criterion that separates AML from MDS. In young patients, underlying, predisposing genetic diseases should be considered (see above).

PROGNOSIS

The median survival varies greatly from years for patients with 5q– or sideroblastic anemia to a few months in refractory anemia with excess blasts or severe pancytopenia associated with monosomy 7; an International Prognostic Scoring System (IPSS; **Table 130-6**) assists in making predictions. Even "low-risk" MDS has significant morbidity and mortality. Most patients die as a result of complications of pancytopenia and not due to leukemic transformation; perhaps one-third will succumb to other diseases unrelated to their MDS. Precipitous worsening of pancytopenia, acquisition of new chromosomal abnormalities on serial cytogenetic determination, increase in the number of blasts, and marrow fibrosis are all poor prognostic indicators. The outlook in therapy-related MDS, regardless of type, is extremely poor, and most patients will progress within a few months to refractory AML.

TREATMENT MYELODYSPLASIA

Historically, the therapy of MDS has been unsatisfactory, but new drugs recently have been approved for this disease. Several regimens appear to not only improve blood counts but to delay onset of leukemia and to improve survival. The choice of therapy for an individual patient, administration of treatment, and management of toxicities are complicated and require hematologic expertise.

Only hematopoietic stem cell transplantation offers cure of MDS. The current survival rate in selected patient cohorts is ~50% at 3 years and is improving. Results using unrelated matched donors are now similar to those obtained using siblings, and patients in their 50s and 60s have been successfully transplanted. Nevertheless, treatment-related mortality and morbidity increase with recipient age. Complicating the decision to undertake transplant is that the high-risk patient, for whom the procedure is most obviously indicated, has a high probability of a poor outcome from transplant-related mortality or disease relapse, whereas the low-risk patient, who is more likely to tolerate transplant, also may do well for years with less aggressive therapies.

MDS has been regarded as particularly refractory to cytotoxic chemotherapy regimens, and as in AML in the older adult, drug toxicity is frequent and often fatal, and remissions if achieved are brief. Low doses of cytotoxic drugs have been administered for their "differentiation" potential, and from this experience, drug therapies have emerged based on pyrimidine analogues. These new drugs are classified as epigenetic modulators, believed to act through a demethylating mechanism to alter gene regulation and allow differentiation to mature blood cells from the abnormal MDS stem cell (although global methylation status has not correlated with clinical efficacy). Azacitidine and decitabine are two epigenetic modifiers frequently used in bone marrow failure clinics. Azacitidine improves blood counts and survival in MDS, compared to best supportive care. Azacitidine is usually administered subcutaneously, daily for 7 days, at 4-week intervals, for at least four cycles before assessing for response. Overall, generally improved blood counts with a decrease in transfusion requirements occurred in ~50% of patients in published trials. Response is dependent on continued drug administration, and most patients eventually will no longer respond and experience recurrent cytopenias or progression to AML. Decitabine is closely related to azacitidine and more potent; 30–50% of patients show responses in blood counts, with a duration of response of almost a year. Decitabine is usually administered by continuous intravenous infusion in regimens of varying doses and durations of 3 to 10 days in repeating cycles. The major toxicity of azacitidine and decitabine is myelosuppression, leading to worsened blood counts. Other symptoms associated with cancer chemotherapy frequently occur. Demethylating agents are frequently used in the high-risk patient who is not a candidate for stem cell transplant. In the lower risk patient, they are also effective, but alternative therapies should be considered.

Lenalidomide, a thalidomide derivative with a more favorable toxicity profile, is particularly effective in reversing anemia in MDS patients with 5q– syndrome; not only do a high proportion of these patients become transfusion independent with normal or near-normal hemoglobin levels, but their cytogenetics also become normal. The drug has many biologic activities, and it is unclear which is critical for clinical efficacy. Lenalidomide is administered orally. Most patients will improve within 3 months of initiating therapy. Toxicities include myelosuppression (worsening thrombocytopenia and neutropenia, necessitating blood count monitoring) and an increased risk of deep vein thrombosis and pulmonary embolism.

Immunosuppression, as used in aplastic anemia, also may produce sustained independence from transfusion and improve survival. ATG, cyclosporine, and the anti-CD52 monoclonal antibody alemtuzumab are especially effective in younger MDS patients (<60 years old) with more favorable IPSS scores and who bear the histocompatibility antigen HLA-DR15.

HGFs can improve blood counts but, as in most other marrow failure states, have been most beneficial to patients with the least severe pancytopenia. EPO alone or in combination with G-CSF can improve hemoglobin levels, but mainly in those with low serum EPO levels who have no or only a modest need for transfusions. Survival does not appear to be improved by G-CSF treatment alone but may be enhanced by erythropoietin and amelioration of anemia. G-CSF treatment alone failed to improve survival in a controlled trial.

The same principles of supportive care described for aplastic anemia apply to MDS. Despite improvements in drug therapy, many patients will be anemic for years. RBC transfusion support should be accompanied by iron chelation to prevent secondary hemochromatosis.

MYELOPHTHISIC ANEMIAS

Fibrosis of the bone marrow **(see Fig. 129-2)**, usually accompanied by a characteristic blood smear picture called *leukoerythroblastosis*, can occur as a primary hematologic disease, called *myelofibrosis* or *myeloid metaplasia* **(Chap. 131)**, and as a secondary process, called