Myelodysplastic Syndromes — Coping with Ineffective Hematopoiesis

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One of the most challenging problems in hematology is the heterogeneous group of disorders that were formally defined as myelodysplastic syndromes by the French–American–British Cooperative Group in 1982. This set of disorders includes idiopathic conditions as well as the secondary or therapy-related forms that develop after exposure to alkylating agents, radiation, or both. Idiopathic myelodysplastic syndromes occur mainly in older persons: the incidence of these syndromes is about 5 per 100,000 persons per year in the general population, but it increases to 20 to 50 per 100,000 persons per year after 60 years of age. Approximately 15,000 new cases are expected in the United States each year, indicating that myelodysplastic syndromes are at least as common as chronic lymphocytic leukemia, the most prevalent form of leukemia in Western countries.

Most patients with these syndromes are initially asymptomatic, and the condition is discovered incidentally on a routine blood count. Others have symptoms of anemia, which is frequently macrocytic but refractory to treatment with folate and vitamin B_{12}. Neutropenia, thrombocytopenia, or both may be found initially or may appear later. Examination of a smear of the peripheral blood reveals such morphologic abnormalities as hypogranulated neutrophils with hyposegmented nuclei (pseudo-Pelger–Huët anomaly) and large platelets. The bone marrow is typically cellular and shows various morphologic abnormalities (marrow dysplasia); in one fifth of patients, however, the bone marrow is hypoplastic — similar to the picture in aplastic anemia.

According to the prevailing dogma, myelodysplastic syndromes are clonal disorders of hematopoietic stem cells with a propensity to evolve into acute myeloid leukemia. Clonal transformation, according to this view, would occur at the level of a committed myeloid stem cell that can give rise to red cells, platelets, and granulocytes and monocytes. Families with an inherited genetic predisposition and multistep progression to a myelodysplastic syndrome and acute myeloid leukemia have been reported[1] but are extremely rare. Whether idiopathic myelodysplastic syndromes are truly clonal proliferations of multipotent stem cells, however, is unclear. The biologic hallmark of these stem cells in myelodysplastic syndromes is, rather, a defective capacity for self-renewal and differentiation. The consequences of this abnormality are probably amplified in the elderly because the aging process itself may not only deplete stem cells, but also alter the marrow microenvironment, particularly in persons with occupational or environmental exposure to chemical and physical hazards. The resulting perturbed interactions between hematopoietic progenitors and marrow stromal cells are probably responsible for ineffective hematopoiesis and may favor the emergence of clones as a secondary phenomenon. Pure erythroid disorders, such as refractory anemia with or without ringed sideroblasts, are essentially due to excessive apoptosis of late erythroid precursors within the bone marrow, a mechanism of anemia known as ineffective erythropoiesis.

The approach to the diagnosis of a myelodysplastic syndrome should begin with the exclusion of more common types of anemia — a process that is of fundamental importance if misdiagnoses are to be avoided. Once common causes of normocytic or macrocytic anemia have been ruled out, the possibility of a myelodysplastic syndrome should be considered. Bone marrow aspiration (to evaluate morphologic abnormalities of hematopoietic precursors), bone marrow biopsy (to assess marrow cellularity and topography), and cytogenetic investigations (to identify nonrandom chromosomal abnormalities) are all mandatory for diagnosis and prognosis.

The World Health Organization (WHO) classification of myeloid neoplasms[2] is a very useful tool for defining the different subtypes of myelodysplastic syndrome (see table). These variants show impressive clinical heterogeneity, ranging from conditions with a near-normal standardized mortality ratio (refractory anemia with erythroid dysplasia only) to entities that are very close to acute myeloid

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WHO Classification and Criteria for the Myelodysplastic Syndromes.*

Disease	Blood Findings	Bone Marrow Findings
Refractory anemia	Anemia, no or rare blasts	Erythroid dysplasia alone, <5% blasts, <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts	Anemia, no blasts	Erythroid dysplasia alone, <5% blasts, ≥15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia	Cytopenias (bicytopenia or pancytopenia), no or rare blasts, no Auer rods, <1 billion monocytes per liter	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines, <5% blasts, no Auer rods, <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts	Cytopenias (bicytopenia or pancytopenia), no or rare blasts, no Auer rods, <1 billion monocytes per liter	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines, <5% blasts, no Auer rods, ≥15% ringed sideroblasts
Refractory anemia with excess blasts, type 1	Cytopenias, <5% blasts, no Auer rods, <1 billion monocytes per liter	Unilineage or multilineage dysplasia, 5–9% blasts, no Auer rods
Refractory anemia with excess blasts, type 2	Cytopenias, 5–19% blasts, occasional Auer rods, <1 billion monocytes per liter	Unilineage or multilineage dysplasia, 10–19% blasts, occasional Auer rods
Myelodysplastic syndrome, unclassified	Cytopenias, no or rare blasts, no Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes, <5% blasts, no Auer rods
Myelodysplastic syndrome associated with isolated del(5q)	Anemia, <5% blasts, platelet count normal to increased	Normal-to-increased megakaryocytes with hypolobated nuclei, <5% blasts, no Auer rods, isolated del(5q)

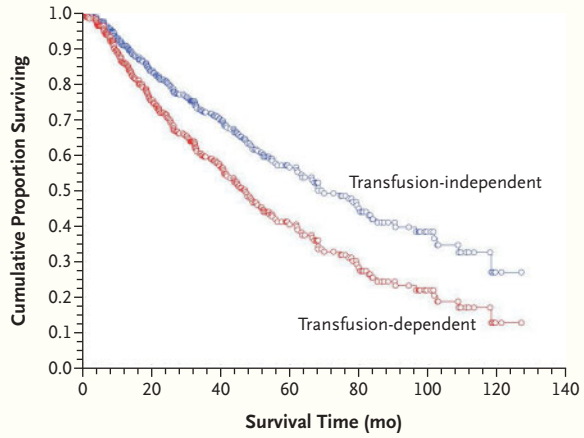
* Information is from Vardiman et al.[2]

leukemia. The International Prognostic Scoring System (IPSS)[3] — based on the percentage of marrow blasts, the cytogenetic pattern, and the number and degree of cytopenias — is useful for predicting survival and the risk of leukemia and facilitates clinical decision making in individual cases.

A risk-adapted treatment strategy is mandatory for disorders that range from indolent conditions lasting years to forms approaching acute myeloid leukemia. Several treatments for myelodysplastic syndromes have been proposed in the past few decades, but only a few have met evidence-based criteria of efficacy. At present, the only treatment that can definitely prolong survival is allogeneic hematopoietic stem-cell transplantation. Approximately one third of patients who receive an allogeneic transplant are cured, but only about 8 percent of all patients with a myelodysplastic syndrome are eligible for such treatment and have a donor. Intensive chemotherapy can be used in patients who have an increase in marrow blasts, but complete remissions are usually achieved only in relatively young patients with favorable cytogenetic characteristics. Azacitidine, which was recently approved by the Food and Drug Administration for the treatment of myelodysplastic syndromes, can be effective in older patients, possibly through the hypomethylation of particular DNA sequences. The remaining potentially effective treatments include immunosuppression with antithymocyte globulin or cyclosporine (or a combination of the two) and stimulation of red-cell production with erythropoietin alone or in combination with granulocyte colony-stimulating factor. These treatments are effective in small subgroups of patients who do not require transfusions and who have low marrow cellularity or a low serum level of erythropoietin.

According to evidence-based practice guidelines,[4] most patients with myelodysplastic syndromes should receive either no treatment or only supportive care. Once anemia is symptomatic, red-cell transfusions and iron chelation are the mainstays of therapy. Dependency on transfusions has an effect on the likelihood of survival (see graph), probably because it is associated with more severe bone marrow inefficiency and because not all transfusion-dependent patients receive adequate iron-chelation therapy.

In this issue of the *Journal,* List and colleagues (pages 549–557) report the treatment of patients with myelodysplastic syndromes and symptomatic anemia with lenalidomide, a thalidomide analogue that is under investigation for the treatment of multiple myeloma. Thalidomide has been used in patients with myelodysplastic syndromes with the aim of exploiting its anticytokine and antiangiogenic



Cumulative Probability of Survival among 374 Patients Given a Diagnosis of Myelodysplastic Syndrome at the Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy, 1992–2002.

Patients were grouped according to whether or not a transfusion requirement developed during their clinical course. The two groups were compared by means of a Cox proportional-hazards regression model with time-dependent covariates. Each patient was considered as part of the transfusion-independent group (blue curve) as long as he or she had no need for blood transfusion and was recategorized in the transfusion-dependent group when a transfusion requirement developed (red curve). Once a regular need for blood transfusion developed, patients had a significantly lower probability of survival (hazard ratio for death, 1.58; P=0.005). The survival curves do not account for the time-dependency of the transfusion requirement.

effects to improve the efficiency of hematopoiesis. Some transfusion-dependent patients can cease requiring transfusions when treated with thalidomide, but a response requires several weeks and treatment is appreciably limited by neurologic toxicity. Lenalidomide does not have this adverse effect and appears to be more suitable than thalidomide for long-term treatment.

The effect of lenalidomide on myelodysplastic hematopoiesis appears to be dual, at least initially: it increases red-cell production and decreases neutrophil and platelet production. This observation cannot be explained by a direct effect on clonal stem cells alone, which should cause parallel changes in peripheral-blood cells. Rather, lenalidomide is likely to modify the marrow microenvironment, and we must assume that the modified hematopoietic milieu favors the efficiency of erythropoiesis while inhibiting granulocytopoiesis and megakaryocytopoiesis. These effects are consistent with an anticytokine activity of lenalidomide and, in turn, with the enhancement of the antiapoptotic activity of erythropoietin on erythroid progenitors and the diminution of the antiapoptotic activity of inflammatory cytokines on myeloid and megakaryocytic progenitors. Apart from these effects, the complete cytogenetic remissions seen in patients with the 5q syndrome who were treated with lenalidomide are impressive, making it difficult to rule out a direct effect of the drug on myelodysplastic clones with the 5q31.1 deletion. It should be noted that the molecular basis of the hypereosinophilic syndrome was identified after this disorder was found to be responsive to imatinib mesylate.[5]

Lenalidomide appears to be a promising treatment for the approximately one third of patients with a myelodysplastic syndrome who have a pure erythroid disorder (according to the WHO classification) or a low-risk condition (according to the IPSS score), and in particular for those with the 5q syndrome. Achievement of transfusion independence and a cytogenetic remission are major accomplishments that might translate into a prolongation of survival. However, the feasibility and adverse effects of treatment need to be defined more precisely, since in the study by List et al., only 21 of the 55 candidates who were screened for eligibility benefited from lenalidomide in terms of a major erythroid response.

In the past 20 years, several therapeutic meteors have passed through the dark sky of treatment for myelodysplastic syndromes, only to disappear. We look forward to prospective studies that can unequivocally confirm the hematologic activity of lenalidomide in these syndromes, and given the current uncertainties, we recommend the use of this drug only within clinical trials.

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