The myelodysplastic syndromes: heterogeneity on many levels

The myelodysplastic syndromes (MDSs) are a heterogeneous group of disorders characterized by ineffective hematopoiesis and a variable risk of transformation to acute leukemia. This heterogeneity, both at the phenotypic and molecular level, is underscored by 2 papers in the current issue of Blood. In the first of these, Steensma and colleagues (page 1518) describe a patient with MDS associated with acquired α-thalassemia. This rare syndrome, referred to as the α-thalassemia myelodysplasia syndrome (ATMDS), is characterized by hypochromic microcytic anemia, anisopoiikilocytosis, markedly reduced α-globin chain synthesis, and substantial amounts (> 10%) of hemoglobin H (beta globin tetramers). While inherited α-thalassemia is typically due to deletions or point mutations affecting the duplicated α-globin genes on chromosome 16, ATMDS has been shown to be due to mutations in a gene called ATRX (alpha thalassemia/mental retardation X-linked homolog).1 This gene on the X chromosome encodes a chromatin-remodeling gene that regulates the expression of a number of genes, including the α-globin genes. Germ line mutations of ATRX have been described and cause a mild α-thalassemia syndrome associated with a mental retardation.2

In the current issue, Steensma and colleagues describe a man with mild anemia, marked microcytosis, hypochromia and anisopoiikilocytosis, and bone marrow studies diagnostic of myelodysplastic syndrome (refractory cytopenia with multilineage dysplasia). Hemoglobin H inclusions were present at low levels (< 1%) in peripheral blood erythrocytes. Globin chain synthetic ratios were consistent with heterozygous α-thalassemia. Marrow chromosome studies revealed complex cytogenetic abnormalities. Fluorescence in situ hybridization (FISH) and Southern blot studies revealed a deletion larger than 1.9 Mb that removed the α-globin cluster from one chromosome 16. Thus, the α-thalassemia phenotype in this patient is due to the deletion of 2 of 4 α-globin genes (genotype αα/αα−−). Interestingly, the red cell changes are more marked than those typically seen in heterozygous α-thalassemia. In addition, the presence of hemoglobin H is also unusual for heterozygous α-thalassemia. It seems likely that this somewhat more severe thalassmic phenotype is due to an interaction between the α-thalassemia deletion and the ineffective erythropoiesis characteristic of a myelodysplastic bone marrow. This is the first report of ATMDS due to deletion of the α-globin gene cluster rather than a mutation in the ATRX gene.

In a second paper, Gattermann and colleagues (page 1499) examined the role of a mitochondrial DNA mutation in MDS. The potential role for mitochondrial DNA in acquired MDS was suggested by the constitutional disorder, Pearson syndrome, in which sideroblastic anemia is accompanied by pancreatic dysfunction. In this disorder a number of deletions in mitochondrial DNA have been described.3 Studies of mitochondrial DNA in acquired MDS have suggested that mutations can be found in up to 50% of patients.4 Other investigators have found that mitochondrial DNA mutations are less widespread in acquired MDS.5 The significance of these mutations and their role in the pathogenesis of MDS remains a subject of ongoing investigation.

Gattermann and colleagues describe a patient with myelodysplastic syndrome (refractory anemia with excess blasts [RAEB]) who was found to have a somatic mutation of mitochondrial transfer RNA (tRNA) in bone marrow cells. Approximately 40% of the mitochondrial DNA molecules in the marrow contained this mutation. The mutation was present at a higher level in marrow and peripheral blood CD34+ cells than in unfractioanted marrow. The mutation was not found in unfractioanted peripheral blood leukocytes or in buccal mucosal cells. These findings suggested that marrow cells carrying the mitochondrial DNA mutation did not contribute to effective hematopoiesis. Thalidomide treatment resulted in improved red cell and platelet production and in a decrease in marrow blast percentage. Interestingly, there was a coincident decrease in the percentage of mutant mitochondrial DNA in the bone marrow. Hematopoietic colony assays were performed using CD34+ cells derived from marrow and peripheral blood. In all cases, mature hematopoietic colonies were composed entirely of cells containing the wild-type mitochondrial DNA. These findings...
Fungal infection in hemato-oncologic patients: better to prevent than to treat?

Invasive fungal infections continue to form a major threat to hemato-oncologic patients, especially in those undergoing allogeneic stem cell transplantation.1 Whereas fluconazole offers effective prophylaxis for candidal infections, up to now no prophylactic measure has proven to be satisfactory against invasive mold infections. By far the most important of the invasive mold infections is aspergillosis, both in terms of frequency of occurrence and prognosis. Prophylaxis trials performed so far have been hampered by the relatively low risk of aspergillosis in the population studied, thereby masking a potential beneficial effect in high-risk subpopulations.2 In this issue, Marr and colleagues (page 1527) describe a carefully conducted prophylaxis trial in patients at high risk of fungal infection. They show that itraconazole is more effective than fluconazole in preventing invasive aspergillosis, as long as patients are able to take the drug. Does this finding mean that we should give itraconazole prophylaxis to these patients or even to all patients at risk for Aspergillus infection?

Because of difficulties in diagnosing and treating invasive fungal infection in severely immunocompromised patients, treatment strategies have concentrated on prophylaxis (preventing infections in all patients at risk), empirical treatment (early treatment in symptomatic patients who may have fungal infection, notably patients with “neutropenic fever”), or preemptive treatment (early treatment in those patients who are likely to have fungal infection). Whereas prophylaxis with itraconazole may now seem the best option at first glance, several questions remain unanswered. First, the time that the patient is at risk is variable and certainly not restricted to the neutropenic episode. In this respect it would be interesting to know how many patients in the study of Marr et al developed aspergillosis during neutropenia as opposed to during treatment with glucocorticosteroids for graft-versus-host disease (GVHD). Second, there is a safety issue. Itraconazole offers its broader antifungal spectrum as an advantage over fluconazole but at the same time is known to have more severe side effects and problematic interactions with many other drugs. In fact, the protocol of the study by Marr et al had to be adjusted because of a possible interaction of itraconazole with cyclophosphamide, and other interactions may still be undetected. This problem of side effects and drug interactions may also be a limiting factor with voriconazole, a new highly potent azole against Aspergillus species. Therefore, what options do we have?

Recently, progress has been made in the diagnosis of early, invasive aspergillosis, using both computed tomography (CT) scanning and serologic techniques. In a recent study, Becker et al3 claimed a positive predictive value of 100% and a negative predictive value of 88% using a combination of CT scanning and Aspergillus galactomannan detection in serum or bronchoalveolar lavage (BAL) fluid. Moreover, new treatment modalities, although still far from perfect, offer a much better treatment outcome of established aspergillosis than before, voriconazole being far superior over conventional amphotericin B.4

The present study of Marr et al certainly provides a rationale for using itraconazole prophylaxis in high-risk patients, such as those receiving allogeneic stem cell transplantation, provided special attention is given to drug interactions and serum levels of itraconazole are measured for step-up (or even step-down) dosing strategies. An alternative approach would be to improve the identification of high-risk patients for primary itraconazole prophylaxis (eg, patients given glucocorticosteroids for GVHD) and in other patients at risk choose for a preemptive strategy with voriconazole, based on new diagnostic techniques, for instance sequential galactomannan assay-guided CT scanning. Which of the 2 strategies is best can only be determined by another carefully developed clinical trial.

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