46

Clonal Disorders of the Hematopoietic Stem Cell

Eunice S. Wang and Nancy Berliner

INTRODUCTION

Malignant transformation involves combined defects in cellular maturation and differentiation. The multistep theory of oncogenesis suggests that these defects are often separable and contribute to a stepwise progression from a normal to a fully transformed cell. The continuous cycling of hematopoietic cells provides a milieu for the development of clonal genetic abnormalities that supports the multistep model. Clonal defects of the hematopoietic stem cell give rise to an array of preleukemic and leukemic disorders. Primary defects of maturation give rise to the myelodysplastic disorders (see Chapter 45), whereas loss of normal control of proliferation results in myeloproliferative disease. All of these disorders are preleukemic, with a variable but definite rate of transformation to acute leukemia.

MYELOPROLIFERATIVE NEOPLASMS

Definition and Pathology

Myeloproliferative neoplasms (MPNs), also known as chronic myeloproliferative diseases (MPDs), are clonal stem cell disorders characterized by leukocytosis, thrombocytosis, erythrocytosis, splenomegaly, and bone marrow hypercellularity. The hallmark of MPNs is the failure of a transformed multipotent stem cell to respond to normal feedback mechanisms regulating hematopoietic cell mass. Stem cells from patients with MPNs demonstrate clonal colony growth in vitro when they are grown in serum without the addition of exogenous cytokines, and this technique has been used as a diagnostic test for MPNs.

MPNs have traditionally been divided into four classic disorders based on the predominant hyperproliferative cell type: polycythemia vera (PV), essential thrombocytosis (ET), primary myelofibrosis (PMF; i.e., idiopathic myelofibrosis or agnogenic myeloid metaplasia), and chronic myelogenous leukemia (CML). Hypereosinophilic syndrome (HES), mast cell disease, and other less common diseases are also included (Table 46-1).

Complications of MPNs arise from the overproduction of one or more lineages in the blood. All can be associated with clonal evolution and blastic transformation to acute leukemia, although with the exception of CML, this is an infrequent and late complication. In most patients with MPNs, the pathogenesis of disease is attributed to dysfunctional kinases.

In CML, a reciprocal translocation between chromosomes 9 and 22 (i.e., Philadelphia chromosome or translocation) results in an Abelson (ABL) leukemia virus–breakpoint cluster region (BCR) fusion protein (BCR/ABL) with constitutive kinase activity. In PV, PMF, and ET, a mutation involving the substitution of a valine for phenylalanine at position 617 (V617F) in the Janus kinase 2 (JAK2) has been identified in most patients and may account for the abnormal growth properties that characterize these stem cell disorders.

Identification of somatic JAK2 mutations in all MPNs has led to clinical development and testing of orally bioavailable small-molecule inhibitors that selectively target dysfunctional JAK2 for the treatment of MPNs. Results from these trials are eagerly awaited.

POLYCYTHEMIA VERA

Definition and Epidemiology

PV, a term meaning increased numbers of red blood cells in the blood, is a syndrome of increased red blood cell mass in the peripheral blood resulting from a clonal multipotent hematopoietic stem cell defect. PV occurs in 1 to 3 of 100,000 people, with a median age at diagnosis of 65 years.

Clinical Presentation

PV is a primary clonal stem cell disorder of unknown origin that is characterized by predominant erythrocytosis associated with other hematopoietic abnormalities. Although one half of patients

TABLE 46-1 WORLD HEALTH ORGANIZATION 2008 CLASSIFICATION OF MYELOID NEOPLASMS

1. Acute myeloid leukemia
2. MDS
3. MPNs
   a. Chronic myelogenous leukemia
   b. Polycythemia vera
   c. Essential thrombocythemia
   d. Primary myelofibrosis
   e. Chronic neutrophilic leukemia
   f. Chronic eosinophilic leukemia, not otherwise categorized
   g. Hypereosinophilic syndrome
   h. Mast cell disease
   i. MPNs, unclassifiable
4. MDS, MPN
5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGF-RA, PDGF-RB, or FGF-R1

FGF-R1, Fibroblast growth factor receptor 1; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; PDGF-RA, platelet-derived growth factor receptor-α polypeptide; PDGF-RB, platelet-derived growth factor receptor-β polypeptide.