Table 13-11 Tyrosine Kinase Mutations in Myeloproliferative Disorders

Disorder	Mutation	Frequency*	Consequences†
Chronic myelogenous leukemia	*BCR-ABL* fusion gene	100%	Constitutive ABL kinase activation‡
Polycythemia vera	*JAK2* point mutations	>95%	Constitutive JAK2 kinase activation
Essential thrombocythemia	*JAK2* point mutations *MPL* point mutations	50% to 60% 5% to 10%	Constitutive JAK2 kinase activation Constitutive MPL kinase activation
Primary myelofibrosis	*JAK2* point mutations *MPL* point mutations	50% to 60% 5% to 10%	Constitutive JAK2 kinase activation Constitutive MPL kinase activation
Systemic mastocytosis	*KIT* point mutations	>90%	Constitutive KIT kinase activation
Chronic eosinophilic leukemia§	*FIP1L1-PDGFRA* fusion gene *PDE4DIP-PDGFRB* fusion gene	Common Rare	Constitutive PDGFRα kinase activation Constitutive PDGFRβ kinase activation‡
Stem cell leukemia‖	Various *FGFR1* fusion genes	100%	Constitutive FGFR1 kinase activation¶

*Refers to frequency within a diagnostic category.
†All stimulate ligand-independent pro-growth and survival signals.
‡Responds to imatinib therapy.
§Associated with Loeffler endocarditis (Chapter 12).
‖Rare disorder originating in pluripotent hematopoietic stem cells that presents with concomitant myeloproliferative disorder and lymphoblastic leukemia/lymphoma.
¶Responds to PKC412 therapy.

classification, details of which are beyond our scope. A prognostic scoring system has been developed that groups patients into 5 major prognostic groups. In brief, worse outcomes are (understandably) predicted by higher blast counts and more severe cytopenias, as well as the presence of multiple clonal chromosomal abnormalities.

The median survival in primary MDS varies from 9 to 29 months, but some individuals in good prognostic groups may live for 5 years or more. Overall, progression to AML occurs in 10% to 40% of individuals and is usually accompanied by the appearance of additional cytogenetic abnormalities. Patients often succumb to the complications of thrombocytopenia (bleeding) and neutropenia (infection). The outlook is even grimmer in t-MDS, which has a median survival of only 4 to 8 months. In t-MDS, cytopenias tend to be more severe and progression to AML is often rapid.

Treatment options are fairly limited. In younger patients, allogeneic hematopoietic stem cell transplantation offers hope for reconstitution of normal hematopoiesis and possible cure. Older patients with MDS are treated supportively with antibiotics and blood product transfusions. Thalidomide-like drugs (see prior discussion in myeloma) and DNA methylation inhibitors improve the effectiveness of hematopoiesis and the peripheral blood counts in a subset of patients. The presence of isolated 5q- is correlated with a hematologic response to thalidomide-like drugs, but as yet response to DNA methylation inhibitors is unpredictable.

Myeloproliferative Disorders

The common pathogenic feature of the myeloproliferative disorders is the presence of mutated, constitutively activated tyrosine kinases or other acquired aberrations in signaling pathways that lead to growth factor independence. Hematopoietic growth factors act on normal progenitors by binding to surface receptors and activating tyrosine kinases, which turn on pathways that promote growth and survival (Chapter 7). The mutated tyrosine kinases found in the myeloproliferative disorders circumvent normal controls and lead to the growth factor-independent proliferation and survival of marrow progenitors. Because the tyrosine kinase mutations underlying the various myeloproliferative disorders do not impair differentiation, the most common consequence is an increase in the production of one or more mature blood elements. Most myeloproliferative disorders originate in multipotent myeloid progenitors, whereas others arise in pluripotent stem cells that give rise to both lymphoid and myeloid cells.

There is a considerable degree of clinical and morphologic overlap among the myeloproliferative disorders. The common features include:

- *Increased proliferative drive* in the bone marrow
- Homing of the neoplastic stem cells to secondary hematopoietic organs, producing *extramedullary hematopoiesis*
- Variable transformation to a spent phase characterized by *marrow fibrosis* and peripheral blood *cytopenias*
- Variable transformation to *acute leukemia*

Certain myeloproliferative disorders are strongly associated with activating mutations in specific tyrosine kinases. This insight and the availability of kinase inhibitors have increased the importance of molecular tests for tyrosine kinase mutations, both for purposes of diagnosis and the selection of therapy. This discussion is confined to the more common myeloproliferative disorders, which are classified based on clinical, laboratory, and molecular criteria. Systemic mastocytosis, a distinctive myeloproliferative disorder that is associated with mutations in the KIT tyrosine kinase, is discussed under disorders of the skin (Chapter 25). The association of various myeloproliferative disorders with specific tyrosine kinase mutations (including rare disorders not discussed here) is summarized in Table 13-11.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is distinguished from other myeloproliferative disorders by the presence of a chimeric *BCR-ABL* gene derived from portions of the *BCR* gene on chromosome 22 and the *ABL* gene on chromosome 9. *BCR-ABL* directs the synthesis of a constitutively active BCR-ABL tyrosine kinase (Fig. 13-32), which

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