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# Focus on myeloproliferative diseases and myelodysplastic syndromes

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## Introduction

Myeloproliferative diseases (MPD) and myelodysplastic syndromes (MDS) are a heterogeneous group of chronic myeloid disorders diagnosed in over 20,000 patients annually in the United States (Tefferi, 2001). The bone marrow (BM) shows normal or increased cellularity in MDS, but is always hypercellular in MPD. Whereas the percentage of blasts at diagnosis ranges from 1%–20% in MDS, it is normal (<5%) in early stage MPD. In MDS, there is morphological evidence of BM myeloid dysplasia usually accompanied by cytopenias, while in MPD there is relatively normal myeloid maturation with an overproduction of circulating myeloid elements and an elevated risk of thrombosis. By contrast, acute myeloid leukemia (AML) is characterized by an excess of bone marrow blasts with defective production of mature cells (Gilliland and Tallman, 2002). MPD and MDS are characterized by clonal hematopoiesis and an increased risk of developing acute leukemia, but the frequency of malignant progression and overall prognosis varies greatly between different subtypes. In the past decade, there have been major advances in our understanding of the pathogenesis and treatment of these diseases.

## Myeloproliferative diseases

### Classification, clinical features, and epidemiology of the MPDs

The World Health Organization (WHO) classification of MPDs (Vardiman et al., 2002) includes chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), chronic idiopathic myelofibrosis (CIMF), and the related disorders chronic eosinophilic leukemia (CEL) and idiopathic hypereosinophilic syndrome (HES) (Table 1). The MPDs each have an incidence of 1–2 cases per 100,000 population per year.

CML is a hematopoietic stem cell MPD that is invariably associated with a *BCR-ABL* fusion gene, usually as a consequence of t(9;22) generating a Philadelphia (Ph) chromosome. CML is characterized clinically by leukocytosis with overproduction of maturing neutrophils, and a triphasic clinical course with chronic, accelerated, and blast crisis stages. Readers are referred to several recent reviews for detailed discussions of the biology and therapy of CML (Faderl et al., 1999; Kantarjian and Talpaz, 2004). Patients with clinical features of CML who lack the *BCR-ABL* fusion are designated as “atypical CML” in the WHO classification, while chronic neutrophilic leukemia (CNL) is a rare disorder characterized by Ph<sup>-</sup> clonal overproduction of mature neutrophils (Table 1).

Since other MPDs have clinical features that can overlap with CML, the *BCR-ABL* fusion should be excluded in all patients. Idiopathic HES is characterized by persistent eosinophilia (>1500/ $\mu$ l) without secondary causes such as malignancy, parasitic infection, or allergy, accompanied by end-

organ damage, including the heart and nervous system. Some HES patients, predominantly male, have clonal eosinophilia often accompanied by anemia, thrombocytopenia, and elevated serum B<sub>12</sub> levels, and probably represent the subset with bona fide MPD. PV is characterized by inappropriate expansion of mature erythroid cells with increased hematocrit and red cell mass, often accompanied by moderate leukocytosis and thrombocytosis, splenomegaly, and an elevated risk of arterial and venous thrombosis. Although no consensus exists for the diagnosis of PV, the WHO modification of the original Polycythemia Vera Study Group criteria is widely used (Tefferi, 2001). Causes of secondary erythrocytosis such as hemoglobinopathies, erythropoietin-secreting tumors, and congenital polycythemia must be excluded. BM cytogenetic studies are normal in most PV patients, with 20%–30% having 20q<sup>-</sup>, +8, or +9. ET is characterized by increased BM megakaryocytes and circulating platelets, normal BM cytogenetics, and an increased incidence of vasomotor symptoms and thrombohemorrhagic events. Reactive causes of thrombocytosis, including infection, malignancy, and iron deficiency, must be excluded. Lastly, CIMF is characterized by clonal myeloproliferation with megakaryocytic hyperplasia accompanied by nonclonal marrow fibroblast proliferation leading to myelofibrosis and extramedullary hematopoiesis, usually with marked splenomegaly and anemia. Risk factors for CIMF include exposure to ionizing radiation, thorium, and benzene, and clonal cytogenetic abnormalities, most frequently 13q<sup>-</sup>, 20q<sup>-</sup>, and +1q, are seen in 30%–40% of patients. The non-CML MPDs have a variable tendency to progress to AML, ranging from 1%–5% in ET and PV to over 20% in CIMF.

### Molecular pathogenesis of MPDs

CML is the best understood MPD. *BCR-ABL* encodes a chimeric polypeptide that joins N-terminal Bcr sequences to C-terminal sequences from c-Abl to generate a cytoplasmic Bcr-Abl fusion tyrosine kinase with constitutively elevated activity. Many lines of evidence implicate Bcr-Abl as the direct cause of CML. Bcr-Abl-expressing cells have high levels of cellular tyrosyl phosphoproteins and constitutive activation of signaling pathways linked to proliferation, survival, and resistance to DNA damage, and expression of Bcr-Abl in murine hematopoietic stem cells induces CML-like myeloproliferative disease in mice (Kantarjian and Talpaz, 2004). The causative role of Bcr-Abl in CML was confirmed by studies of imatinib mesylate (also called Gleevec or STI571), a 2-phenylaminopyrimidine compound that is a competitive inhibitor of ATP binding to the Abl, c-Kit, and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Imatinib inhibits proliferation and induces apoptosis in Bcr-Abl-expressing cells, suppresses Ph<sup>+</sup> myeloid BM colony formation (Druker et al., 1996), and induces hematologic and cytogenetic responses in most CML patients (O'Brien et al., 2003).

**Table 1.** WHO classification of MPD and MDS

Disorder	Peripheral blood	Bone marrow
<b>Myeloproliferative diseases</b>		
Chronic myeloid leukemia (CML)	Leukocytosis, neutrophilia with left shift, basophilia, thrombocytosis, ↓ LAP score	Hypercellular, <5% blasts (chronic phase), no Auer rods, Ph <sup>+</sup> and/or BCR-ABL <sup>+</sup>
Chronic neutrophilic leukemia (CNL)	Clonal neutrophilia without left shift	Granulocytic hyperplasia w/o dysplasia, Ph <sup>-</sup> and BCR-ABL <sup>-</sup>
Polycythemia vera (PV)	Erythrocytosis w/↓serum Epo, leukocytosis w/ ↑ PRV-1, thrombocytosis, ↑ LAP score	Hypercellular, +endogenous erythroid colonies, Ph <sup>-</sup> and BCR-ABL <sup>-</sup>
Essential thrombocythemia (ET)	Thrombocytosis w/nl hematocrit	Megakaryocytic hyperplasia w/o dysplasia, nl Fe stores, Ph <sup>-</sup> and BCR-ABL <sup>-</sup>
Chronic idiopathic myelofibrosis (CIMF)	Anemia w/teardrop erythrocytes, platelets and leukocytes ↑ or ↓	Nonclonal fibrosis, extramedullary hematopoiesis, Ph <sup>-</sup> , ± clonal cytogenetic abnl
Chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES)	Clonal eosinophilia >1500/μl	Hypercellular with ↑ eosinophil precursors, ± FIP1L1-PDGFRα fusion, Ph <sup>-</sup> and BCR-ABL <sup>-</sup>
Chronic myeloproliferative disease, unclassifiable	Leukocytosis with excess myeloid cells	Myeloid hyperplasia w/o dysplasia, ± clonal cytogenetic abnl [eg t(9;12)]
<b>Myelodysplastic/myeloproliferative syndromes</b>		
Chronic myelomonocytic leukemia (CMML)	Monocytes >1000/μl, ± eosinophilia, blasts <5% (CMML-1) or 5-19% (CMML-2)	Dysplasia in 1 or more lineages, <20% blasts, ± clonal cytogenetic abnl [eg t(5;12), t(5;7)]
Juvenile myelomonocytic leukemia (JMML)	Monocytes >1000/μl, blasts <5%	Myeloid hyperplasia, GM-CSF hypersensitivity, KRAS2, NRAS, PTPN11, and NF1 mutations
Atypical CML	Leukocytosis, neutrophilia, often with anemia/thrombocytopenia	Often w/dysplasia in neutrophils or multilineage, Ph <sup>-</sup> and BCR-ABL <sup>-</sup>
MDS/MPD, unclassifiable	Leukocytosis, blasts <5%	Hypercellular, dysplasia in 1 or more lineages
<b>Myelodysplastic syndromes</b>		
Refractory anemia (RA)	Anemia, no or rare blasts	Erythroid dysplasia only, <5% blasts, <15% RS
Refractory anemia with ringed sideroblasts (RARS)	Anemia, no blasts	Erythroid dysplasia only, <5% blasts, ≥15% RS
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia of 2 or 3 lineages, no or rare blasts, no Auer rods, monocytes <1000/μl	Dysplasia >10% of cells in ≥2 myeloid lines, no Auer rods, <5% blasts, <15% RS
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenia of 2 or 3 lineages, no or rare blasts, no Auer rods, monocytes <1000/μl	Dysplasia >10% of cells in ≥2 myeloid lines, no Auer rods, <5% blasts, ≥15% RS
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias, <5% blasts, no Auer rods, monocytes <1000/μl	Uni- or multi-lineage dysplasia, 5-9% blasts, no Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias, 5-19% blasts, ± Auer rods, monocytes <1000/μl	Uni- or multi-lineage dysplasia, 10-19% blasts, ± Auer rods
Myelodysplastic syndrome with del(5q)	Anemia, <5% blasts, platelets nl or ↑	Nl to ↑ megakaryocytes w/hypolobulated nuclei, <5% blasts, no Auer rods, isolated del(5q)
Myelodysplastic syndrome, unclassifiable (MDS-U)	Cytopenias, no or rare blasts, no Auer rods	Unilineage dysplasia in neutrophils or megakaryocytes, <5% blasts, no Auer rods

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A subset of patients with the myeloproliferative variant of HES/CEL and elevated serum tryptase levels also respond to imatinib (Klion et al., 2003; Pardanani et al., 2003b). Cryptic internal deletions of chromosome 4q12 that fuse *PDGFRA* with *FIP1L1* are found in most of these patients (Cools et al., 2003a). A point mutation in the FIP1L1-PDGFRα catalytic domain rendering the fusion kinase insensitive to imatinib was identified in a responding HES patient who relapsed, solidifying its pathogenetic role (Cools et al., 2003b). Systemic mastocytosis (SM), characterized by clonal mast cell proliferation, hepatosplenomegaly, and urticaria, is classified separately from the MPDs (Vardiman et al., 2002). However, some patients with SM and eosinophilia respond to imatinib and express FIP1L1-PDGFRα (Pardanani et al., 2003a), while others have an activating D816V mutation in *c-KIT* and are imatinib-unresponsive (Zermati et al., 2003). Further molecular genetic studies are required to clarify the relationship between these clinical syndromes.

In contrast to CML and HES, the causative molecular defects in PV, ET, and CIMF are unknown. The central pathophysiological abnormality in PV is red cell production that is independent of erythropoietin (Epo), the hormone that normally regulates erythropoiesis. In PV, serum Epo levels are low, and BM erythroid progenitors form Epo-independent colonies in methylcellulose cultures (Correa et al., 1994). These endogenous erythroid colonies (EEC) are diagnostic of the disease. The molecular basis of EEC is unknown, but it is likely to be downstream of the cell surface receptor for Epo (Epo-R), which is not mutated and has normal expression and affinity for Epo. PV erythroid cells demonstrate abnormal tyrosine kinase and phosphatase signaling, increased expression of Bcl-X<sub>L</sub>, and decreased expression of c-Mpl, while aberrant transcription of PRV-1, a member of the uPAR receptor family (Temerinac et al., 2000), has been documented in granulocytes from PV patients. However, none of these abnormalities is diagnostic of or the

cause of PV. Studies of rare pedigrees of familial PV have suggested a dominant multistep mode of inheritance, involving both loss- and gain-of-function mechanisms (Kralovics et al., 2003). Similar to PV, BM megakaryotic precursors (CFU-Meg) from ET patients form colonies in the absence of exogenous thrombopoietin (Tpo), but spontaneous CFU-Meg can also be found in CML and PV. There is no evidence for mutations in the genes for c-Mpl or Tpo, and ET patients have normal or even decreased plasma Tpo levels, possibly reflecting increased Tpo clearance due to the elevated circulating platelet mass. In CIMF, the underlying abnormality is clonal hematopoiesis with chronic myeloproliferation and expansion of atypical megakaryotes that secrete growth factors, including TGF- $\beta$  and Tpo, responsible for BM fibrosis and increased vascularity (Reilly, 1997).

#### **Recent advances in the biology and therapy of MPDs**

The therapy of CML is evolving rapidly (reviewed in Kantarjian and Talpaz, 2004). Imatinib has quickly replaced interferon- $\alpha$  as the treatment of choice in chronic phase CML (O'Brien et al., 2003), but initial enthusiasm has been tempered by the realization that molecular remissions are rare with imatinib (Hughes et al., 2003), possibly because quiescent Ph<sup>+</sup> stem cells are insensitive to the drug (Graham et al., 2002). In addition, acquired resistance is frequent in advanced CML and can arise from *BCR-ABL* gene amplification or from point mutations that render the kinase less sensitive to the drug (Gorre et al., 2001). Lastly, there is concern about clonal Ph<sup>-</sup> cytogenetic abnormalities that develop in some imatinib-treated patients, although their clinical significance is unknown (Loriaux and Deininger, 2004). Second-generation Abl kinase inhibitors with increased potency and activity against some imatinib-resistant Bcr-Abl mutants are in clinical testing (Shah et al., 2004), but drug resistance is likely to be a persistent problem. There is much interest in identifying signaling pathways contributing to myeloproliferation and disease progression in CML that could be targeted to prevent or overcome resistance to Abl kinase inhibitors. Ras, phosphatidylinositol 3-kinase, and mammalian target of rapamycin are activated by Bcr-Abl, and drugs inhibiting these pathways have activity in preclinical models of *BCR-ABL* leukemia (Hoover et al., 2002; Mohi et al., 2004). Src family kinases are also activated by Bcr-Abl and targeted by dual Abl-Src inhibitors (La Rosee et al., 2002), but may be involved principally in blast crisis rather than chronic phase CML (Hu et al., 2004). Dysregulated Wnt signaling leading to aberrant self-renewal may contribute to progression of CML to myeloid blast crisis (Jamieson et al., 2004). Despite the clinical success of imatinib, allogeneic hematopoietic stem cell transplantation (alloHSCT) remains the only known curative treatment for CML, which is due to a potent graft-versus-leukemia (GvL) effect mediated by donor lymphocytes. Novel approaches to increase GvL responses include patient vaccination or generation of donor cytotoxic T cells against antigens such as proteinase-3 or WT-1 that are overexpressed in CML BM (Molldrem et al., 2002).

Specific therapy of HES with imatinib should be guided by molecular studies whenever possible. Imatinib responses often occur at daily doses as low as 100 mg, reflecting the high sensitivity of PDGFR $\alpha$  to the drug. Some HES patients, particularly those with elevated serum Troponin T levels, develop acute myocarditis upon initiation of imatinib therapy (Pardanani et al., 2003b), which usually responds to corticosteroids.

Therapy of the other MPDs is empiric and largely aimed at ameliorating symptoms and preventing complications. In PV,

the mainstay of therapy is controlling the hematocrit with phlebotomy or hydroxyurea to prevent hyperviscosity and stroke. Low-dose aspirin therapy can decrease the incidence of thrombotic complications without increasing the risk of hemorrhage (Landolfi et al., 2004). The anti-megakaryocyte agent anegrelide has been used to control thrombocytosis, but there is no evidence that this affects the incidence of thrombosis. In ET, the overall prognosis is good, and the mainstay of treatment is prevention of vasomotor and thrombohemorrhagic events by controlling the platelet count with hydroxyurea and/or anegrelide. In CIMF, the prognosis is much worse, and the only curative treatment is alloHSCT for younger patients, where engraftment is not a problem despite the marrow fibrosis. The anemia of CIMF is managed symptomatically with transfusions and iron chelation therapy, while some patients respond to androgens, corticosteroids, or thalidomide. Imatinib is generally ineffective in these MPDs, and new approaches to therapy are needed.

#### **Myelodysplastic syndromes and related chronic myeloid disorders**

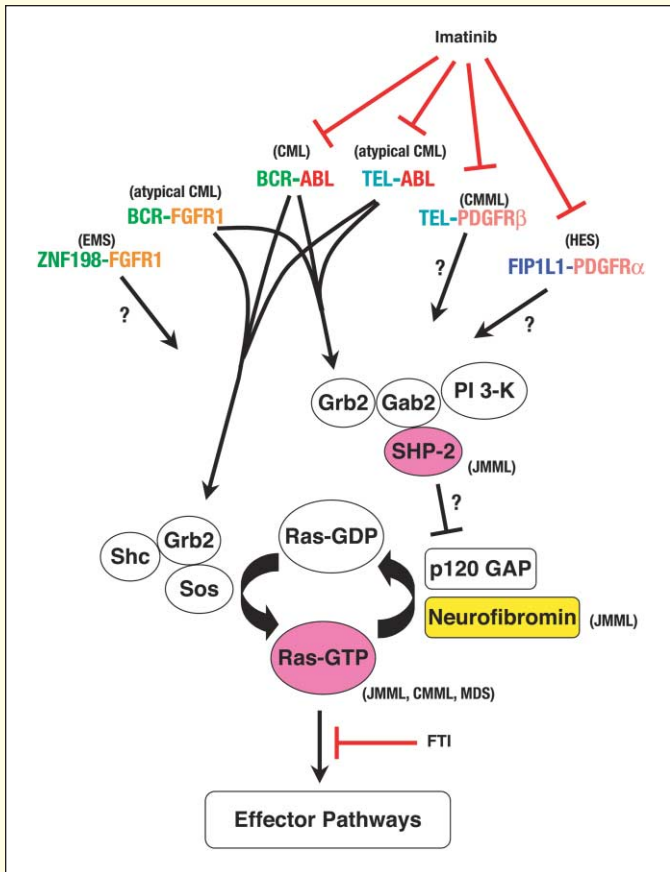
##### **Classification, clinical features, and epidemiology of MDS**

The wide spectrum of clinicopathologic syndromes and our limited understanding of molecular pathogenesis have impeded efforts to accurately classify MDS. The WHO modification of the original FAB classification system incorporated molecular and cytogenetic data, defined patients with >20% BM blasts as having AML, and created a new category of MDS/MPD overlap that includes juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML). The prognosis of MDS varies widely, and an International Prognostic Scoring System (IPSS) is useful in predicting outcomes (Greenberg et al., 1997). MDS will probably continue to be subdivided as the underlying molecular lesions are discovered.

Table 1 summarizes clinical and pathologic features of the MDS syndromes. The incidence of MDS rises progressively with age, and many patients present with symptoms of cytopenia such as infection, bleeding, or fatigue. In contrast, patients with proliferative MDS subtypes may have fever, splenomegaly, and leukocytosis. Rather than the chromosomal translocations that predominate in AML, chromosomal deletions including monosomy 5/del(5q), monosomy 7/del(7q), and del(20q) are detected in many MDS patients. Whereas most patients with MDS present with normo- or hypercellular marrows, some have dysplasia in the context of reduced cellularity. Demonstrating an MDS-associated clonal cytogenetic abnormality helps to distinguish this syndrome from aplastic anemia. The 8p11 myeloproliferative syndrome (EMS) is not explicitly included in the current WHO classification, but is characterized by myeloproliferation with eosinophilia and high-grade non-Hodgkin's lymphoma in association with balanced translocations of chromosome band 8p11.

Therapy-induced MDS (t-MDS) is a distinct clinicopathologic entity. Affected patients typically present with cytopenia 3–7 years after receiving alkylating agents and/or radiotherapy to treat a primary cancer (Smith et al., 2003). BM cytogenetics frequently show monosomy 5/del(5) and/or monosomy 7/del(7). The prognosis is dismal. Patients treated with topoisomerase II inhibitors are also at increased risk of developing secondary myeloid malignancies, but with the notable exception of MDS patients with t(11;16), most develop de novo AML rather than MDS (Smith et al., 2003). Children with neurofibromatosis type 1 (NF1) or Noonan syndrome (NS) have an increased incidence





**Figure 1.** Aberrant signal transduction in MPD and MDS

Many of the genetic lesions found in MPD and MDS lead to production of mutant proteins that are components of cellular signaling networks that modulate Ras-GTP levels (Sawyers and Denny, 1994). Fusion protein-tyrosine kinases and the diseases in which they are found are shown at the top. Myeloproliferation induced by Bcr-FGFR1, Bcr-Abl, and Tel-Abl depends on direct binding to the adaptor protein Grb2, which can activate Ras directly through Sos or indirectly through Gab2 (Sattler et al., 2002) and SHP-2, which may inhibit proteins that negatively regulate Ras, such as Ras-GAP and NF1. Pathways leading to Ras activation from the other fusion kinases are not yet defined. Activating mutations (purple) in SHP-2 and Ras and loss (yellow) of NF1 are observed in JMML, CMML, and MDS. Imatinib targets a subset of the fusion tyrosine kinases (top), while farnesyltransferase inhibitors (FTI) target the common Ras pathway (bottom) and also likely inhibit other farnesylated signaling proteins (Downward, 2003).

of JMML, while those with Fanconi anemia (FA), congenital neutropenia (CN), Shwachman Diamond syndrome (SDS), and familial thrombocytopenia (FTP)/AML syndrome are at increased risk of developing cytopenic subtypes of MDS.

**Molecular pathogenesis of the proliferative subclass of MDS/MPD**

Aberrant signal transduction is strongly implicated in the proliferative MDS subtypes. Myeloid progenitors from JMML patients are hypersensitive to granulocyte-macrophage colony-stimulating factor in vitro. The *NF1* tumor suppressor gene encodes a GTPase activating protein that negatively regulates Ras signaling, and the normal *NF1* allele is frequently deleted in JMML cells from children with NF1 (Side et al., 1997). Germline missense mutations in *PTPN11*, which encodes the SHP-2 tyrosine phosphatase, are found in nearly all NS patients with JMML,

while somatic *PTPN11* mutations are detected in about 35% of sporadic JMML (Tartaglia et al., 2003). Some of these mutations disregulate SHP-2 phosphatase activity by destabilizing an autoinhibitory interaction, and thereby increase signaling to Ras and other downstream effectors (Tartaglia et al., 2004). Overall, ~85% of JMML specimens show mutations in *KRAS2*, *NRAS*, *NF1*, or *PTPN11* that are largely mutually exclusive, arguing strongly that hyperactive Ras initiates this MDS. This is supported by studies of *Nf1*, *Kras*, and *Ptpn11* mutant mice, all of which develop myeloid disorders resembling JMML and CMML (Araki et al., 2004; Braun et al., 2004; Chan et al., 2004; Le et al., 2004). In CMML, *KRAS2* and *NRAS* mutations are found in ~40% of patients, while other cases of CMML with translocations involving 5q33 express fusions of platelet-derived growth factor receptor (PDGFR)  $\beta$  with various partner proteins, including TEL (Golub et al., 1994). While activating mutations in the receptor tyrosine kinase FLT3 are frequent in AML (Gilliland and Tallman, 2002), they are rare in MDS and usually associated with leukemic progression. Finally, expression in murine bone marrow of either EMS- or CML-associated fusions involving the *FGFR1* gene on 8p11 recapitulates the human diseases (Roumiantsev et al., 2004). This work and previous studies of Bcr-Abl suggest that engagement of Ras and other pathways via the adaptor proteins Grb2 and Gab2 plays a central role in the myeloproliferative phenotype (Sattler et al., 2002). Hence, as previously suggested by Sawyers and Denny (Sawyers and Denny, 1994), a central theme underlying CML and the proliferative MDS subtypes is dysregulated signaling leading to Ras activation (Figure 1).

**Molecular pathogenesis of cytopenic MDS**

In contrast to the proliferative subtypes of MDS, we have little understanding of the pathophysiology underlying peripheral cytopenia in the context of the hypercellular bone marrow that is characteristic of RA, RA with ringed sideroblasts or excess blasts, 5q- syndrome, and t-MDS. MDS BM cells have elevated levels of apoptosis that might contribute to ineffective hematopoiesis and cytopenias. Recurrent deletions of 5q31, 7q22, and 20q12 in MDS suggest that loss-of-function of unidentified myeloid tumor suppressor genes within these chromosomal regions contributes to the pathogenesis of MDS. Haploid dosage of genes in these intervals might also contribute to MDS, as germline haploinsufficiency of *RUNX1* is the cause of FTP/AML syndrome (Song et al., 1999). Somatic *RUNX1* mutations have also been reported recently in de novo and therapy-induced MDS, particularly in patients with monosomy 7/del(7q) (Harada et al., 2003). Among the inherited MDS subtypes, the FA pathway is a multicomponent DNA damage response system (D'Andrea and Grompe, 2003). Mutations in the *ELA2* gene cause most cases of CN (Dale et al., 2000), but the mechanisms of neutropenia or progression to MDS, which is often associated with somatic mutations in the G-CSF receptor, are unknown. Mutations in the *SBDS* gene, encoding a protein of unknown function, are associated with SDS (Boocock et al., 2003). Transformation to MDS in FA, CN, and SDS is frequently associated with complete or partial monosomy 7, suggestive of common genetic pathways with sporadic MDS. Retroviral expression in murine BM of the transcription factor MLL-CBP, the product of t(11;16) in t-MDS (Lavau et al., 2000), and of EVI1, a zinc finger protein aberrantly expressed in some cases of MDS (Buonamici et al., 2004), induces cytopenic MDS-like syndromes that should provide useful model systems for further study.

### Recent advances in the therapy of MDS

The management of MDS must be individualized, and the IPSS is useful for deciding which patients might benefit from intensive treatment. Conventional high dose chemotherapy is both toxic and largely ineffective. AlloHSCT may cure MDS; however, most patients are poor transplant candidates due to advanced age, coexisting disease, or lack of a suitable donor. Nonmyeloablative alloHSCT is being explored as an alternative. The response of MDS cytopenias to hematopoietic cytokines is variable; the combination of Epo and G-CSF induces neutrophil responses in most patients and erythroid responses in 40%–45%. While imatinib is effective in cases of CMML with PDGFR $\beta$  fusion proteins (Figure 1), the lack of validated targets in most types of MDS has limited the development of molecular therapeutics. Farnesyltransferase inhibitors, which have modest efficacy, probably do not inhibit Ras signaling in vivo (Downward, 2003). Aberrant DNA methylation is widespread in MDS BM specimens, and treatment with methyltransferase inhibitors may restore a more normal pattern of growth by reactivating genes silenced by epigenetic mechanisms in the MDS clone. Recently approved by the FDA for MDS, 5-azacytidine (5-aza) induces hematologic improvements in 60% and delays progression to AML (Silverman et al., 2002), although there was a much lower rate of complete remissions (7%). The relationship between alterations in genomic DNA methylation and clinical responses to 5-aza in MDS is uncertain. The immunomodulatory agent Revlimid (CC5013) has significant erythropoietic remitting activity in low-intermediate risk MDS, improving anemia and normalizing cytogenetic and dysplastic features (List et al., 2003). Other therapies that are being explored in MDS include arsenic trioxide, histone deacetylase inhibitors, and antiangiogenic agents.

### Future challenges

MPD and MDS have played a central role in the evolving paradigm of defining molecular targets through laboratory analysis of primary cancer cells, using this knowledge to identify therapeutic agents that interfere with target proteins, and monitoring the biochemical effects of treatment in the malignant cells. A major challenge in those diseases where the pathogenesis is understood will be extrapolating the therapeutic responses to targeted drugs into long-term remissions or cures. This may demand a combination of targeted therapies, immunotherapy, and strategies to eliminate the rare population of stem-like neoplastic cells that maintain the disease in vivo. For the majority of MPD and MDS where the underlying defects are not known, significant progress may depend on identifying the causative mutations, which will require careful bench-to-bedside studies of human patients and animal modeling. Translating these pathophysiological insights into improved treatments will require new approaches to identify patients who are likely to benefit from targeted therapies and to enroll them into clinical trials.

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