New insights into the pathogenesis and treatment of chronic myeloproliferative disorders
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Purpose of review
The classic BCR-ABL negative myeloproliferative disorders are at a crossroads of rapidly evolving pathogenetic understanding, leading to changes in diagnostic criteria and potentially targeted therapy. This review focuses on the implications of these changes relative to current standards.

Recent findings
The V617F activating mutation of Janus kinase 2, and associated parallel mutations, is at least partially responsible for myeloproliferation (and potentially vascular events) associated with myeloproliferative disorders. It is unclear whether the mutation facilitates progression to the blast phases of myeloproliferative disorders.

Summary
The high prevalence of the V617F mutation of Janus kinase 2 and associated mutations in myeloproliferative disorders (>95% in polycythemia vera and about half of patients with essential thrombocytopenia and primary myelofibrosis) has led the World Health Organization to alter the diagnostic criteria for these myeloproliferative disorders, and these changes are reviewed. Current therapy for myeloproliferative disorders remains largely based on preventing vascular events and symptomatic control, with allogeneic stem cell transplantation for high-risk patients. Investigational approaches to myeloproliferative disorders involve targeting the bone marrow microenvironment and DNA hypermethylation. Phase I clinical testing of inhibition of Janus kinase 2, active in vitro, began with several agents in 2007; the results are highly anticipated.

Keywords
essential thrombocythemia, Janus kinase 2 inhibitors, JAK2-V617F, myeloproliferative disorders, polycythemia vera, primary myelofibrosis

Introduction
The Philadelphia chromosome (or BCR-ABL) negative chronic myeloproliferative disorders (MPDs), first described by Dameshek in 1951 [1], are currently in a period of rapid discovery of pathogenetic mechanisms. This period of rapid improvement in mechanistic understanding is leading to similar changes in diagnostic criteria and hopefully will yield improved targeted therapies. The MPDs have classically included the disorders of polycythemia vera, essential thrombocythemia, and primary myelofibrosis (PMF), but even our preconceived understanding of the diagnostic and therapeutic differences between these disorders are evolving rapidly.

The watershed moment for MPDs occurred in 2005 with the heavily publicized discovery of the V617F mutation in Janus kinase 2 (JAK2) [2–5]. This latter point mutation, in the pseudo-kinase domain of JAK2 [a key component of the cell growth and differentiation JAKsignal transducer and activator of transcription (STAT) pathway], leads to constitutive activation of the pathway. This mutation joined the pantheon of constitutively active tyrosine kinases identified as playing a role in myeloid neoplasms, including BCR-ABL in chronic myeloid leukemia, FIP1L1-PDGFRA (Fip1-like 1/platelet-derived growth factor receptor-α chain) for chronic eosinophilic leukemia and systemic mastocytosis, the D816V mutation in Kit for systemic mastocytosis, among many others [6]. Additional genetic mutations with potential pathogenetic implications have also been described, including the W515L/K mutation in MPL (the receptor for thrombopoietin; in 5% of PMF and 1% of essential thrombocythemia cases) [7] and alternative mutations in exon 12 of JAK2 in some of those polycythemia vera patients previously identified as wild type for JAK2 [8**]. So, what is the impact of our improved understanding of MPD biology on the diagnostic process?
The diagnosis of the BCR-ABL negative MPDs has always been limited by the absence of a ‘gold standard’, an absolute molecular marker. This latter deficiency has led to a series of clinical/pathological diagnostic criteria that rely upon features that are helpful in distinguishing an MPD from a reactive state, an alternative myeloid malignancy, and an alternative MPD diagnosis. These criteria usually were the easiest to apply to overt MPD cases but not uncommonly would leave others with uncertainty. The World Health Organization has taken a lead role in refining diagnostic criteria for MPDs, and the current World Health Organization criteria [9] for polycythemia vera, essential thrombocythemia, and PMF are undergoing a revision [10] to incorporate the diagnostic implications of the new wave of mutations (such as the JAK2V617F). These criteria have evolved and become more straightforward now that an objective marker such as the JAK2V617F is being incorporated (Fig. 1), removing many antiquated features of diagnosis that sought only to exclude secondary causes of cellular proliferation.

Current therapy for myeloproliferative disorders: a summary

The MPDs are associated with a variable period of risk for vascular events and long-term risk for transformation to either an overt myelofibrotic phase or death. Currently available therapies have rarely been able to influence this natural history beyond palliating symptoms or decreasing the risk for vascular events. Given these challenges, how should MPD patients be optimally managed?

After the appropriate diagnosis of an MPD is established, or sometimes even suspected, patients must be stabilized for immediate coagulopathies from severe erythrocytosis, thrombocytosis, or concurrent or pre-existing thrombotic events. Management decisions will then partially flow from the clinician’s estimation of overall disease prognosis and separate estimation of risk for vascular events. In patients with essential thrombocythemia and polycythemia vera, high-risk patients are defined as either having a prior vascular event or being older than 60 years.

Figure 1 Diagnostic criteria

Presented are current [9] and proposed [10] World Health Organization (WHO) diagnostic criteria for the myeloproliferative disorders of polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). CML, chronic myeloid leukemia; ET, essential thrombocythemia; Hb, hemoglobin; JAK, Janus kinase; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; pO2, oxygen tension.
and low-risk patients are those who lack either of these features (and a platelet count <1000 × 10^9/l). Intermediate risk essential thrombocythemia and polycythemia vera lack these prior features but have cardiovascular risk factors. Potential newly identified vascular risk factors include leukocytosis at diagnosis (at least in polycythemia vera: >15 × 10^9/l [11]) or high JAK2^{V617F} mutation allele burden [12]. If and how these new factors should be included in modeling MPD vascular risk is not yet known and requires further study. The MPDs carry a variable prognostic outlook. PMF (and post-essential thrombocythemia/polycythemia vera myelofibrosis) carry the worst prognosis, with median survival rivaling that of many lethal solid malignancies.

Various prognostic features can help to stratify suspected outcomes in PMF patients [13], including anemia [14], karyotypic abnormalities [15], age, presence of circulating blasts [14], and markedly increased angiogenesis in the marrow [16]. Additionally, newer robust prognostic data can be obtained by evaluating peripheral blood anemia, markedly abnormal leukocyte counts (<4 or >30 × 10^9/l), thrombocytopenia (<100 × 10^9/l), and/or monocytosis [17]. There is no proof that the newly described JAK2^{V617F} abnormality has a prognostic impact on PMF patients, or that mutation status has relevance in the decision regarding the timing of stem cell transplantation [18].

**Short term therapeutic plan**

The immediate therapeutic concerns in MPD patients at presentation are both adequate prophylaxis against vascular events and palliation, when possible, of MPD symptomatology. Available therapies for both essential thrombocythemia and polycythemia vera in this regard have been successful only in decreasing the risks for thrombotic or hemorrhagic (i.e., vascular) events. Management of polycythemia vera patients includes control of erythrocytosis (by phlebotomy) and, when no contraindication exists, use of low-dose aspirin [19]. The degree to which a patient must be phlebotomized has been questioned, with traditional dogma suggesting a goal hematocrit of below 42% for women and 45% for men. Recent retrospective analysis of vascular events of patients on the European Collaborative Low Dose Aspirin Trial has suggested that modestly higher targets (perhaps hematocrit up to 55%) may not increase the risk for vascular events [20]). Whether goal hematocrits should be changed for polycythemia vera is a question that should be addressed by appropriately designed trials.

What about myelosuppressive therapy for managing the MPDs? Hydroxyurea was shown in a randomized study to aid in the prevention of thrombotic events in patients with high-risk essential thrombocythemia [21]. The UK Medical Research Council Primary Thrombocytocemia-I [22] trial compared, in a randomized manner, hydroxyurea and anagrelide (both along with low-dose aspirin) in patients with essential thrombocythemia. It revealed hydroxyurea plus aspirin to be superior with regard to preventing arterial events, hemorrhage, and transformation to post-essential thrombocythemia myelofibrosis. Therefore, standard front-line therapy for high-risk essential thrombocythemia and polycythemia vera, who require platelet-lowering therapy, is hydroxyurea. Although concerns linger as to whether hydroxyurea accelerates an MPD toward leukemic transformation, this has never been proven when it is used as a single agent [23]. The use of pegylated interferon-2α has exhibited intriguing activity, and potentially improved tolerability, over traditional interferon for especially polycythemia vera [24]. How interferon compares with hydroxyurea for control of vascular events has not yet been studied in a randomized trial.

Palliating symptoms in MPD patients can include therapies for pruritus (antihistamines and selective serotonin reuptake inhibitors), erythromelalgia (aspirin), and fatigue (exercise). Cytopenias have improved in subsets of patients with erythropoietin supplementation [25], androgens [26], and/or corticosteroids. Similarly, use of nonspecific myelosuppressive regimens such as oral hydroxyurea [27] and cladribine [28] have all been reported to confer palliative reduction in painful splenomegaly.

**Long term therapeutic plan**

Currently, no therapy has been shown to be curative, to alter natural history, or to prolong survival in MPD patients, except for allogeneic stem cell transplantation. The long-term therapeutic plan for MPD patients, and particularly those with PMF (and post-essential thrombocythemia/polycythemia vera myelofibrosis), can be divided as follows: observation; proceeding directly to allogeneic stem cell transplantation; and enrollment in an appropriate clinical trial. Observation as a medical plan implies continued vigilance and therapy for prevention of vascular events and appropriate therapy for palliation of MPD symptoms. Observation is most appropriate for those patients with low-risk PMF, and controlled essential thrombocythemia and polycythemia vera. Additionally, observation requires continued vigilance of the patient’s disease status for disease progression to a point at which a clinical trial would be appropriate or stem cell transplantation would be considered.

The choice and role of allogeneic stem cell transplantation for MPD patients remains an evolving issue. Among the MPDs, allogeneic stem cell transplantation is most attractive for high-risk PMF, given that this MPD is the most likely to decrease survival among those afflicted. A recent report described a 3-year survival of 58% in a group of 56 PMF (and post-essential thrombocythemia/polycythemia vera myelofibrosis) patients (age 10–66 years), with a 32%
nonrelapse mortality rate [29]. The significant toxicity of full allogeneic transplantation in PMF led to exploration of the use of reduced intensity conditioning trials [30]. The latter trials have been encouraging in terms of decreased nonrelapse mortality and increasing ages of those successfully transplanted. Allogeneic transplantation still carries a significant risk for graft-versus-host disease (at least 33%), however, and the exact role and benefit depend on the long-term prognosis of the patient. The significant risks associated with any of the stem cell transplantation procedures make it difficult to justify this therapy for essential thrombocythemia and polycythemia vera, given the overall good prognosis of these patients.

Novel therapeutic approaches for myeloproliferative disorders (non Janus kinase-2 targets)

In addition to ineffective erythropoiesis, PMF is characterized by a prominent bone marrow stromal reaction occurring in early stages of the disease, which has been associated with increased marrow expression of profibrogenic and pro-angiogenic cytokines such as transforming growth factor-β, platelet-derived growth factor, tumor necrosis factor-α, basic fibroblast growth factor, and vascular endothelial growth factor [31]. Therapies aimed at molecular targets involved in the aforementioned pathogenetic pathways represent the cornerstone of current clinical trials in PMF.

The group of immunomodulatory cytokine inhibitory and anti-angiogenic agents, collectively known as immunomodulatory drugs (IMIDs), have shown promise in the MPDs, and most specifically in PMF and post-essential thrombocythemia/polycythemia vera myelofibrosis. Initial pilot studies with thalidomide in PMF were dose escalating in nature, beginning at doses of 100 mg/day [32]. Subsequent low-dose (50 mg/day) thalidomide with a prednisone taper [33] resulted in significant responses in terms of anemia (67%), thrombocytopenia (75%), and splenomegaly (33%); however, there were no definitive improvements in marrow or karyotypic abnormalities. Subsequently, lenalidomide (a second-generation, more potent, cytokine-inhibitory IMID) was evaluated in 68 patients with symptomatic PMF, with overall response rates of 22% for anemia, 33% for splenomegaly, and 50% for thrombocytopenia [34], but with improved marrow histology in responders. Mirroring the activity of lenalidomide in del(5q) myelodysplastic syndrome, PMF patients with an abnormality in chromosome 5 appear to respond best to this agent [35]. Given the promising results obtained with lenalidomide, a randomized, placebo-controlled, international clinical study to determine the activity of pomalidomide (20000-fold more potent than thalidomide in inhibiting tumor necrosis factor-α, with or without a prednisone taper) in PMF and post-essential thrombocythemia/polycythemia vera myelofibrosis is currently under way with results eagerly anticipated.

Multiple other attempts to target the bone marrow stromal reaction in PMF (post-essential thrombocythemia/polycythemia vera myelofibrosis) with angiogenesis inhibitors [agents such as vatalanib (PTK787/ZK 222584)] [36], fibrogenesis inhibitors (GC-1008) [37], farnesyl transferase inhibitors [38], and DNA hypermethylation are underway in a series of ongoing trials (Table 1) [24,34,37,39–46].

The next generation of targeted therapy for PMF will move beyond agents targeting the stromal reaction, or cytokines, to agents aimed at the aberrant clone and constitutively active proliferative stimuli with agents directed against vascular endothelial growth factor [39] and those that inhibit the proteasome [40]. Tyrosine kinase inhibitors have been of great benefit to patients when a molecular target exists (i.e. imatinib mesylate and chronic myeloid leukemia). The effects of current tyrosine kinase inhibitors in MPDs have been modest to toxic [47], with trials investigating second-generation agents (such as dasatinib) [41] ongoing.

Targeting the Janus kinase 2 family of myeloproliferative disorder mutations

The next generation of targeted therapy for PMF will move beyond agents that target the stromal reaction, or cytokines, to agents aimed at the aberrant clone and constitutively active proliferative stimuli. Although the currently identified molecular defects do not fully explain many issues of MPD pathogenesis, they provide an exciting and hopefully more fruitful therapeutic target. There have already been multiple reports of agents in development that have demonstrated ability to inhibit the aberrant JAK2V617F, along with wild-type JAK2, such as TG101209 [42], Go6976 [43], erlotinib [44], MK0457 [45], CEP-701 [46] (now in a clinical study), and Z3 [48]. Intriguingly, in primary cells from patients with wild-type JAK2, who have the MPLW515L/K mutation, growth inhibition can similarly be accomplished by JAK2 inhibitors such as TG101209 [42]. These latter observations suggest the possibility that a growth dependence on the JAK-STAT pathway may exist even in JAK2 wild-type MPD patients, and agents that target this pathway may be active regardless of JAK2 mutation status. This hypothesis is further supported by the continual discovery of aberrations in this pathway, as in exon 12 of the JAK2 gene in JAK2V617F negative polycythemia vera patients [8**].

Challenges as we enter the era of JAK2 inhibitors for PMF and MPD patients are several. First, who are the
ET, essential thrombocythemia; FLT3, FMS-related tyrosine kinase 3; JAK2, Janus kinase 2; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera.

Table 1 Investigational medical therapies for the BCR-ABL negative myeloproliferative disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Agent</th>
<th>Class/type of drug</th>
<th>Route</th>
<th>Phase</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Immunomodulatory agents</td>
<td>Pegylated interferon-2α</td>
<td>Immunomodulatory agent</td>
<td>Subcutaneous</td>
<td>I/II</td>
<td>[24]</td>
</tr>
<tr>
<td>PV/ET</td>
<td>Lenalidomide + prednisone</td>
<td>Immunomodulatory agent</td>
<td>Oral</td>
<td>I/II</td>
<td>[34]</td>
</tr>
<tr>
<td>PMF/post-ET/PV MF</td>
<td>CC-4047 +/- prednisone</td>
<td>Immunomodulatory agent</td>
<td>Oral</td>
<td>Ongoing</td>
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<tr>
<td>Targeting the stromal reaction</td>
<td>GC-1008</td>
<td>Pan-specific human anti-TGF antibody</td>
<td>Intravenous</td>
<td>I/II</td>
<td>[37]</td>
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<td>DNA hypomethylating agents</td>
<td>Bevacizumab</td>
<td>Anti-VEGF monoclonal antibody</td>
<td>Intravenous</td>
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<td>PMF/post-ET/PV MF</td>
<td>Azacitidine</td>
<td>Hypomethylating agent</td>
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<td>Targeting apoptosis</td>
<td>Decitabine</td>
<td>Hypomethylating agent</td>
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<td>Kinase inhibitory agents</td>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
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<td>PMF/post-ET/PV MF</td>
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<td>Kinase inhibitor</td>
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<td>Preclinical</td>
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<td>Aurora kinase inhibitor</td>
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most appropriate candidates for agents with uncertain safety profiles, given that there are many patients with JAK2V617F-positive essential thrombocythemia and polycythemia vera, with a good natural history [49], who will be seeking these agents? Second, although there are many agents that may have ability to inhibit wild-type JAK2, we must proceed with caution because few have the desired specificity for the JAK2 itself, let alone JAK2V617F. This opens up the possibility of many undesired toxicities related to the inhibition of additional tyrosine kinases. Additional challenges are inherent in the process of clinical research; how do we effectively choose which candidate agents from preclinical testing truly merit clinical testing, and how do we properly design trials to truly test optimal dose and schedule of these agents? Indeed, there is concern that significant potential for type II error exists for agents whose response we are uncertain how to evaluate, and that we could prematurely discard beneficial agents by making incorrect assumptions regarding the chronology or rapidity of response.

Conclusion

What effects can we expect to observe from the inhibition of JAK2 (no medication is likely to strictly inhibit the JAK2V617F)? As we look at MPD therapeutic goals, will uncertainty exists as to whether inhibition of JAK2 will accomplish these goals because the exact role of the JAK2V617F mutation in disease progression or development of acute leukemia or PMF blast phase remains unclear [50]. The observation that JAK2 mutant MPD patients have the potential to develop acute leukemia from a JAK2 wild-type clone [51] calls into question the role of this mutation in disease progression. Therefore, the impact that JAK2 inhibition will have on disease progression (i.e. none, decrease, or increase) is quite uncertain and will require close long-term monitoring of patients taking JAK2 inhibitors, in order to be certain no adverse effect arises from the use of these agents. Finally, if beneficial, will the JAK2 inhibitors lead to a cure? This is unlikely at this juncture, but an outcome that parallels the efficacy of imatinib for CML [52] in terms of short-term and long-term control of the disease would be greatly welcomed by physician and patient alike.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 141–142).

Myeloid disease


This is a key report that describes novel mutations accounting for JAK2-V617F negative patients with polycythema vera.


This report presents the proposed 2008 World Health Organization diagnostic criteria for the MPDs.


This paper presents a good discussion of the impact that JAK2-V617F allele burden has on MPD disease phenotype.


33 Leukemia 2000; 96:3374–3380.


