MYELOPROLIFERATIVE DISEASES

Clinical, pathological and molecular features of the chronic myeloproliferative disorders: MPD 2005 and beyond

JAN JACQUES MICHIELS

Department of Hematology, University Hospital Antwerp, Belgium, and Goodheart Institute, Hematology, Hemostasis and Thrombosis Research Rotterdam, The Netherlands

Abstract
The combined use of bone marrow histopathology, biomarkers and clinical features has the potential to diagnose, stage and distinguish early and overt stages of ET, PV and idiopathic myelofibrosis, that has an important impact on prognosis and treatment of MPD patients. As the extension of the PVSG and WHO for ET, PV and agnogenic myeloid metaplasia (AMM), a new set of European clinical and pathological (ECP) criteria clearly distinct true ET from early or latent PV mimicking true ET, overt and advanced polycythemia vera (PV), and from thrombocytemia associated with prefibrotic, early fibrotic stages of chronic megakaryocytic granulocytic metaplasia (CMGM) or chronic idiopathic myelofibrosis (CIMF). Cases of atypical MPD and masked PV are usually overlooked by clinicians and pathologists. Bone marrow biopsy will not differentiate between post-PV myelofibrosis versus so-called classical agnogenic myeloid metaplasia. The recent discovery of the JAK2 V617F mutation can readily explain the trilinear megakaryocytic, erythroid and granulocytic proliferation in the bone marrow, but also the etiology of the platelet-mediated microvascular thrombotic complications at increased platelet counts and red cell mass in essential thrombocytemia and polycythemia vera.

Introduction
In the 1980s and 1990s, the German pathologists Burkhardt et al. Georgii et al. [2–4] and Thiele et al. [5–10] have described typical histopathological features from bone marrow biopsy material for the diagnosis and classification of each of the 3 different Ph-negative MPDs ET, PV and AMM. In 1997, we introduced histopathology from bone marrow biopsies as a diagnostic clue and pathognomonic feature of each of the MPDs ET, PV and megakaryocytic granulocytic myeloid metaplasia (CMGM) [11–13]. Thiele & Kvasnicka extended the Rotterdam criteria for ET, PV and added the Cologne criteria for MGM or chronic idiopathic myelofibrosis (CIMF) [14,15]. This concept was taken over by the WHO criteria for true ET, classical PV, and prefibrotic and fibrotic stages of MGM or CIMF [16]. To overcome the shortcomings of the PVSG and WHO criteria, a new set European clinical and pathological (ECP) criteria for the diagnosis ET, PV and CIMF was proposed by Michiels and Thiele [17], which allows to differentiate between the early stages of ET, PV and MGM, to detect prefibrotic and various degrees of fibrosis in PV and MGM and to classify the early, overt and advanced stages of PV and MGM or CIMF, that have major prognostic and therapeutic implications.

Diagnosis and classification of the myeloproliferative disorders: MPD
The inclusion and exclusion criteria for the diagnosis of true ET according to WHO [55] and ECP [17] are identical except platelet count of $>600 \times 10^9$ l$^{-1}$ according the WHO, and $>400 \times 10^9$ l$^{-1}$ according the ECP (Table I).

A typical bone marrow picture for true ET affects mainly of the megakaryocytic cell lineage and shows increased numbers of loosely clustered enlarged, mature megakaryocytes with hyperploid staghorn-like nuclei together with normal cellularity, erythropoiesis, and granulopoiesis, no increase of reticulin fibrosis, and there is no peripheral blood or bone marrow and cytogenetic evidence of CML, PV, MGM, CIMG, MDS or reactive thrombocytosis.

The Rotterdam criteria of PV proposed by the Thrombocytemia Vera Study Group (TVSG) extend the PVSG criteria by including histopathology from bone marrow biopsies (Figure 1) [14]. A typical
picture in the bone marrow diagnostic for classical PV is featured by increase of clustered enlarged mature megakaryocytes comparable to ET, and a moderate to marked increased cellularity, erythropoiesis and granulopoiesis, the so-called trilinear myeloproliferation [16,17]. The megakaryocytes in PV may have a rather pleomorphic appearance with wide ranges of sizes including small and giant forms. In our experience a typical PV picture of the bone marrow is seen in classical PV, in erythrocythemia or idiopathic erythrocytosis, in early or latent PV and in masked PV [14–22]. The combination of a typical PV picture, increased red cell mass, high hematocrit and one of the B criteria is consistent with classical PV according the WHO [16] and PVSG criteria. A typical PV picture of the bone and increased red cell mass, high hematocrit but normal platelet count and spleen size is consistent with stage 1 erythrocythemia, is not consistent with PV according to WHO and will be overlooked by the PVSG criteria. A typical PV bone marrow picture with normal red cell mass and hematocrit but with increased platelet count is consistent with ET [13]. This prompted Thiele to define this entity as early (latent) PV (Figure 1 bottom right) [14]. In our experience, early or latent PV usually presents with microvascular disturbances at platelet count in excess of $400 \times 10^9 \text{L}^{-1}$, increased LAF score, low serum EPO, spontaneous EEC and no or slight splenomegaly. The combination of a typical PV picture, normal red cell mass, normal platelet but slowly progressive splenomegaly, granulocytosis or even slight anemia is not consistent with either ET, PV but with atypical or unclassifiable MPD or masked PV [13]. Such cases may present with thrombotic complications including splanchnic vein thrombosis (Budd-Chiari syndrome, portal, splenic or mesenteric vein thrombosis) [24,25], or masked PV [26,27], which all typically show spontaneous EEC as the clue to the atypical presentation of MPD. Such cases of atypical MPD and masked PV are overlooked by clinicians and pathologists and may comprises about one quarter of patients with initially a typical PV picture of the bone marrow and usually will progress to so-called classical CIMF without overt PV. At time of classical CIMF bone marrow biopsy will not differentiate between post-PV myelofibrosis versus so-called classical agnogenic myeloid metaplasia. In this regard, we reported a case of primary myelofibrosis with splenomegaly in 1971 in a 61-year old man [28]. The spleen size had progressed to 7 and 13 cm below the costal margin (18 and 23 cm length diameter on scan) respectively associated with progressive anemia increase of platelet count from normal to $811 \times 10^9 \text{L}^{-1}$ and increase of leukocytes from normal to $24 \times 10^9 \text{L}^{-1}$ during a follow-up period of 18 years. Sequential bone marrow biopsies showed normal cellularity, fine reticuline fibers grade 1 according to Baumeister [29], and an increase of clustered mature megakaryocytes with hyperploid nuclei in 1971, 1978 and 1982, but hypercellularity, coarse reticulin and collagen fibrosis (dry tap) and increased clustered megakaryocytes in 1985 and 1989 [28].

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>$&gt;400 \times 10^9 \text{L}^{-1}$</th>
<th>$&gt;600 \times 10^9 \text{L}^{-1}$</th>
<th>Rotterdam &amp; ECP WHO</th>
<th>Rotterdam &amp; WHO &amp; ECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Increase of dispersed or loosely clustered, predominantly enlarged mature megakaryocytes with hyperlobulated nuclei and mature cytoplasm, normal cellularity, no or borderline increase of reticulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion</td>
<td>No proliferation or immaturity of granulo- or erythropoiesis</td>
<td>No peripheral blood, bone marrow and cytogenetic evidence of PV, CML, CIMF, MDS or reactive thrombocytosis</td>
<td>ECP</td>
<td>Rotterdam &amp; WHO &amp; ECP</td>
</tr>
</tbody>
</table>

Table I. The Rotterdam, the ECP and the WHO criteria for the diagnosis of true ET

A1 Raised red cell mass
male $>36 \text{mL/kg}$
female $>32 \text{mL/kg}$
A2 Absence of any cause of secondary erythrocytosis by clinical and laboratory investigations
A3 Histopathology of bone marrow biopsy increase of:
a. cellularity, pancytopenia
b. enlarged megakaryocytes with hyperploid nuclei; clusters of megakaryocytes
c. reticulin fibers (optional)

B1 Thrombocytosis
Platelet count $>400 \times 10^9 \text{L}^{-1}$
B2 Granulocytes $>10 \times 10^9 \text{L}^{-1}$ and/or raised neutrophil alkaline phosphatase score of $>100$ in the absence of fever or infection
B3 Splenomegaly on palpation or isotope/ultrasound scan
B4 Erythroid colony formation in absence of EPO: spontaneous EEC

A1 + A2 + A3 is consistent with early stage PV (so-called ”idiopathic erythrocytosis”)
A1 + A2 + A3 + any one from category B establishes overt PV
A3 + B1 is consistent with essential thrombocytopenia
A3 + B3 and/or B4 is consistent with a primary myeloproliferative disorder

Figure 1.
Bone marrow biopsy clearly differentiates between PV and congenital or secondary erythrocytosis with a sensitivity and specificity of more than 95% near to 100% as recently by Thiele et al. [18,19]. In congenital and secondary erythrocytosis, in which increased erythropoiesis is present, the number, size, morphology and distribution of megakaryocytes in bone marrow smears and biopsies remain normal [19,20,22].

The third category of chronic myeloproliferative disorders (CMPD) is usually termed agnogenic myeloid metaplasia or chronic idiopathic myelofibrosis (CIMF), but various other designations have been used such as primary myelofibrosis, myelofibrosis with myeloid metaplasia (MMM) etc [30–33]. AMM, CIMF or MMM is generally defined as a clinicopathological entity not preceded by any other MPD, CML or MDS and characterized by various degrees of anemia, splenomegaly, a leuko-erythroblastic blood picture with tear drop-shaped erythrocytes and various degrees of bone marrow fibrosis or osteosclerosis, and thus by definition disregarding the early non-fibrotic stage of the disease [16,30–33]. In the late 1970s and early 1980s Thiele et al. [5,6] and Georgii et al. [2] drew attention to an authentic dual megakaryocytic granulocytic myeloproliferation (CMGM) as a separate pathological entity among the MPDs. This condition has been labeled in 1996 as chronic megakaryocytic myeloproliferation (CMGM) by Georgii et al.[4] and described in detail as prefibrotic CIMF by Thiele et al. [34–39] to distinguish this entity from ET. Prefibrotic CMGM or CIMF according to the Cologne [14,15], WHO [16] and ECP [17] criteria is a mixed proliferation of increased granulopoiesis and megakaryopoiesis without or with early fibrosis but dominated with immature giant megakaryocytes which are conspicuously enlarged due to increase of nuclear as well as cellular size with bulky and irregular roundish-shaped nuclei, so-called cloud-like nuclei is typical of CMGM (Table II) [34–39]. The prefibrotic and early fibrotic stages of CMGM or CIMF are frequently associated with pronounced thrombocythemia, without a leuko-erythroblastic blood picture, normal or increased LAF-score and no or minimal splenomegaly (Table II) [34–39], which according to the PVSG criteria are to be diagnosed as ET [38].

The semiqualitative grading of reticulin and collagen fibrosis has recently been improved and standardized. In each of the MPDs, myelofibrosis (MF) can be graded from 0 to 3 [40]. Myelofibrosis is not a feature of true ET according to the WHO or ECP. Very few ET patients will develop myelofibrosis during long-term follow-up [4]. Myelofibrosis is present in only a minority of PV patients at time of diagnosis, but all stages of myelofibrosis have been observed during long-term follow-up [43]. There is a conflict of opinion and observer disagreement with regard to the classification and natural history of prefibrotic and early CMGM or CIMF and its differentiation from true ET [41]. Those cases within prefibrotic CMGM or CIMF with slight maturation defect of enlarged megakaryocytes are featured by a rather slowly progressive myelofibrosis with slight splenomegaly or anemia and a life expectancy near to normal similar as in PV. Prefibrotic MGM or CIMF with slight dysmegakaryopoesis may precede classical CIMF for 5 to more than 10 years [42]. Discussions between clinicians and pathologists reveal that diagnostic differentiation between true ET and thrombocythemia as the presenting feature of prefibrotic CMGM (or CIMF) with slight maturation defect of enlarged clustered megakaryocytes and no or slight increased cellularity is subjective with a high inter-observer disagreement between pathologists.

Clinical, laboratory and pathological features of the MPDs in 2005 and beyond

Comparing the WHO/ECP with the PVSG criteria for the diagnosis of ET show that the PVSG criteria fail to distinguish ET from early PV mimicking ET and fail to distinguish ET from early stages of thrombocythemia associated with CMGM or CIMF (Table III) [42–44]. The diagnostic guidelines of the World Health Organisation (WHO) explicitly include bone marrow pathology as a positive criterion for the distinction of true ET, early and overt PV and prefibrotic or early fibrotic myeloid metaplasia or CIMF. In consideration of disease-related complications occurring at low platelet counts, the arbitrarily chosen limit for platelet count (>600×10^10) by the PVSG and WHO has been reduced to 400×10^10 by the European clinical and pathological (ECP) criteria for ET. The PVSG clinical criteria for ET, when compared to the WHO and ECP criteria, include true ET, early PV mimicking ET and thrombocythemia as the presenting feature of prefibrotic or early fibrotic MGM or CIMF (Table III) [42–44]. The ECP criteria clearly differentiate PV from SP, and ET from reactive thrombocytosis, initial PV and prefibrotic MGM or CIMF. The PVSG and the WHO criteria for the diagnosis of PV in Table IV used increased red cell as the main requisite, which is a very crude and overlook by definition early PV mimicking true ET (stage 0) and the erythrocryhemic phase (stage 1) of PV, formerly labeled as idiopathic erythrocytosis. It became apparent that spontaneous endogenous erythroid colony formation (EEC) and PRV-1 expression are the hall mark of PV, and about 50% of ET patients are EEC positive or PRV-1 positive. The reports on EEC/PRV-1 positive ET according to the PVSG very likely represents early or initial stages of PV because of a typical PV bone marrow picture. The cohorts of early stage 0 and 1 PV
and the overt stage 2 PV patients are featured by spontaneous EEC, positive PRV-1, low serum EPO levels and a typical PV bone marrow picture. The cohorts of early stage 0 and 1 PV and the overt stage 2 PV patients are featured by EEC and PRV-1 positivity, low serum EPO levels and a typical PV bone marrow picture (Table IV) [18–27]. Both the early (stage 0 and 1) and overt (stage 2) PV patients are at high-risk for potential minor and major vascular complications, because they present with elevated platelet count mimicking true ET [21–23]. About 50% of ET patients, diagnosed according to the PVSG criteria, have elevated levels of PRV-1 expression together with low serum erythropoietine (Epo) levels, and Epo independent erythroid colony formation (EEC) [45–48]. EEC/PRV-1 positive ET according to PVSG criteria is associated with a higher risk of developing microvascular and major thrombotic com-

Table II. The Cologne, the WHO and the European clinical and pathological (ECP) criteria for the diagnosis and staging of MGM, CIMF or MMM-AMM

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Pathological criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Megakaryocytic and granulocytic myeloproliferation (MGM) and no or relative reduction of erythroid precursors. Abnormal clustering and increase in atypical giant to medium sized megakaryocytes containing bulbous (cloud-like) hypolobulated nuclei and definitive maturation defects.</td>
</tr>
<tr>
<td>B1</td>
<td>Staging of myelofibrosis (MF)</td>
</tr>
<tr>
<td></td>
<td>Prefibrotic stage CIMF: no reticulin fibrosis</td>
</tr>
<tr>
<td>C</td>
<td>Early CIMF: slight reticulin fibrosis</td>
</tr>
<tr>
<td>MF-0</td>
<td>Manifest CIMF: marked increase in reticulin and slight to moderate collagen fibrosis</td>
</tr>
<tr>
<td>MF-1</td>
<td>Overt CIMF: advanced collagen fibrosis with optional osteosclerosis</td>
</tr>
</tbody>
</table>

The combinations of A1+B1 establish CIMF—any other criterion confirms CIMF/AMM

Table III. Clinical, pathological and molecular features of true ET, initial PV mimicking ET and false ET when the PVSG and WHO/ECP criteria are compared

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Hereditary ET</th>
<th>True ET</th>
<th>Initial PV mimicking ET</th>
<th>ET-MGM Prefibrotic Early Fibrotic CIMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>&lt;0.001</td>
<td>20–30</td>
<td>20–30</td>
<td>50–60</td>
</tr>
<tr>
<td>Serum EPO</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased ♦</td>
<td>Normal</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>♦♦♦♦</td>
<td>♦♦♦♦</td>
<td>♦♦♦</td>
<td>♦♦♦♦</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>N</td>
<td>N</td>
<td>N/</td>
<td>N/#</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>N</td>
<td>N</td>
<td>N/*</td>
<td>N/#</td>
</tr>
<tr>
<td>Bone marrow:</td>
<td>ET picture</td>
<td>ET picture</td>
<td>PV picture</td>
<td>MGM picture</td>
</tr>
<tr>
<td>Cellularity myelopoise</td>
<td>N</td>
<td>N</td>
<td>♦♦♦♦</td>
<td>♦♦♦♦</td>
</tr>
<tr>
<td>Erythropoiesis</td>
<td>N</td>
<td>N</td>
<td>♦♦♦♦</td>
<td>♦♦♦♦</td>
</tr>
<tr>
<td>Megakaryocytes</td>
<td>Normal</td>
<td>enlarged/giant and mature</td>
<td>megakaryocytes</td>
<td>abnormal Clonality</td>
</tr>
<tr>
<td>JAK2V617F</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+ versus –</td>
</tr>
<tr>
<td>EEC</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>PVR-1</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
PRV-1-positive ET comprises a pathophysiologically distinct subgroup of ET patients that is at risk for the development of thrombotic complications and for emergence of PV that may reflect early or initial PV [48]. Early or initial PV according to WHO [16] and ECP [17] criteria is typically featured by a PV picture in the bone marrow, positive results for EEC and PRV-1, and/or low serum Epo levels, and a much higher thrombotic risk, which is related to increase of hypersensitive platelet counts (thrombocytopenia) and slightly increased values for hematocrit up to 0.50, and therefore candidates for low dose aspirin and phlebotomy (Table II).

The clonal and molecular etiology of ET, PV and MGM

The MPDs represent clonal proliferation of the hematopoietic stem cells [49–53]. The clonal nature is found in nearly all PV and CIMF patients, while a variable proportion of ET patients are polyclonal. A key observation since 1974 [19] is the spontaneous growth of EEC as a hallmark of PV, but also found in about half of ET patients and in a proportion of CIMF patients [24–27,45,55]. Apart from spontaneous EEC, PV bone marrow cells are hypersensitive to insulin growth factor-1 (IGF-1) [56–58]. IGF-1 sensitivity ratios reached as high as 20,000 times the no and this level of cytokine hypersensitivity in the erythroid lineage of PV is specific to IGF-1. In addition, PV bone marrow cells are hypersensitive but to a less extent, to other hematopoietic growth factors including IL-3, GM-CSF and SCF. Spontaneous endogenous megakaryocyte colonies (EMC) (CFU-Meg) in the absence of exogenous growth factors has been described in ET patients [59–62]. The median TPO sensitivity ratios were more than 50 times the normal and this was highly specific with respect to cytokine, disease and cell lineage, suggesting a lineage restricted hypersensitivity of hematopoietic progenitors to normal endogenous TPO in thrombocytopenia (ET and early PV mimicking ET) [62]. In patients with AMM/CIMF clear evidence of hypersensitivity was found for SCF, a cytokine active in several different cell lineages [63]. These results prompted Axelrad to propose a model that the clinicopathological phenotypes of the clonal MPDS (ET, PV and CIMF) are related to, and perhaps determined by specific hypersensitivities of their progenitor cells to normal endogenous cytokine: EEC-IGF-1 hypersensitivity for PV, TPO-hypersensitivity for thrombocytopenia (ET and early PV mimicking ET) and GM-CSF and SCF hypersensitivity for granulocytosis in PV and for CIMF/AMM respectively. In the studies of Pahl et al. PVR-1 gene expression has been detected in nearly all PV and in about half of the ET patients, who also demonstrated spontaneous EEC, and there was a near to 100% concordance between EEC and PRV-1 positivity in PV and ET patients as well as EEC negativity and normal PRV-1 expression in ET patients [64–67]. The EEC/PRV-1 positive disease may present clinically as an ET (early PV mimicking PV), that will develop into PV, as PV or as a variant of CIMF having quickly passed the hypercellular polycythemic stage (Tables III and IV).
The discovery of JAK2 V617F gain of function mutation by Vainchenker in June 2004 has become a real evolutionary event for a better understanding towards an unifying concept on the molecular etiology for ET, PV, and MGM, or CIMF as well as for the clinical manifestations of platelet-mediated thrombosis, for the increased red cell mass complicated by major and for secondary myelofibrosis [68]. JAK2 plays an essential role in hematopoiesis by mediating signals from several hematopoietic cytokines including EPO, TPO, IL-3, G-CSF, GM-CSF etc [69–71]. The JAK2 mutation makes the mutated hematopoietic progenitor cells hypersensitive for TPO, EPO, IL-3, G-SCF and GM-CSF and thereby leading to growth advantage of the mutated above the normal trilinear hematopoietic cells in the bone marrow. The discovery of the JAK2 V617F mutation by Vainchenker [68] was rapidly confirmed by several investigators [72–76]. According to the PVSG criteria, half of the ET and MF patients and the majority of PV patients have the mutated the JAK2 allele. By pooling the currently available data that were generated by DNA sequencing, the frequency of JAK2 V617F is 73% in PV, in ET, and 43% in CIMF. A much higher frequency of JAK2 in MPD (97% in PV, 57% in ET and 50% in CIMF) was described in one study that used allele-specific polymerase chain reaction (PCR) analysis in addition to sequencing. The mutation was absent in more than 600 healthy controls, in patients with Ph1+CML, and in patients with reactive thrombocytosis. The mutation has been found rarely in CML, MDS, hyper-eosinophilic syndrome, chronic neutrophilic leukemia, chronic myelomonocytic leukemia, but somewhat more frequent in CML-like MDS and unclassified MPD. The acquired JAK2 V617F mutation is located on chromosome 9p. A minority of ET and about half of the PV and MF patients have both JAK2 alleles mutated, which is the consequence of mitotic recombination between homologous chromosomes 9p in a cell heterozygous for V616F and results in loss of heterozygosity of chromosome 9p (9pLOH). The 9pLOH is a second genetic event of duplication of chromosome 9p bearing the mutated JAK2 and therefore homozygous.

The JAK2 V617F mutation affects the trilinear hematopoietic bone marrow cells and is detectable in platelets, erythroblasts and granulocytes. The gain of function mutation is in line with the concept of Dameshek that all “stops” to blood production in the bone marrow seem to have been pulled out by one factor JAK2 V617F causing, due to hypersensitivity of hematopoietic progenitor cells to growth factors, trilinear myeloproliferation. The hypothesis may be that heterozygous JAK2 mutation with low activity may be enough for megakaryocyte proliferation with increase of hypersensitive platelets (ET) with no or slight increase of erythropoiesis (initial early PV), and that homozygous JAK2 mutation with moderate to high activity surely will produce pronounced megakaryocyte, erythroid or even granulocytic proliferation with the clinical pictures of PV, atypical granulocytic leukaemia, unclassifiable MPD with secondary myelofibrosis [76–78]. The sequential occurrence of heterozygous and homozygous V617F mutation can readily explain the spontaneous megakaryocyte and erythroid colony formation (EEC), and the hypersensitivity of granulocyte precursors to growth factors (increased PRV-1 expression) with the sequential production of increased hypersensitive platelets as a first step, increased hematocrit as a second step aggravating the microvascular disturbances of thrombocythemia into the macrovascular complications of polycythemia vera. Similarly, the sequential occurrence of heterozygous and homozygous V617F mutation can also explain the dual granulocytic megakaryocytic proliferation associated with increased leukocyte activation and production (leukocytethmia) and secondary myelofibrosis without features of PV because of progressive splenomegaly. Two main questions to be answered are the following. First, are cases of true ET either clonal or polyclonal positive or negative for JAK2 V617F. Second, are cases of prefibrotic or early fibrotic CMGM or CIMF JAK2 V617F positive, are additional genetic defect needed for progressive MPD disease or do indepen-
dent genetic defects give rise to JAK2 negative and Philadelphia chromosome negative PV, and AMM with predicted poor prognosis (Figure 2). The genetic aetiology and natural history, as well as the pathophysiology of clinical manifestations and the haematological peripheral blood and bone marrow features of JAK2 positive and JAK2 negative MPDs have to be determined in a large prospective study of newly diagnosed and previously untreated Philadelphia chromosome negative MPD patients to be followed-up for 5 to more than 10 years [79].

References


[25] Briere BJH 2005


[52] Harrison CN, Gale RE, Machin SJ, Linch DC, A large proportion of patients with the diagnosis of essential thrombocythemia do not have a clonal disorder and may be at lower risk of thrombosis. Blood 1999;93:417–424.


[77] Steensma DP, Dewald M, Lasho TL, Powell HL, McClure RF, Levine RL et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both atypical myeloproliferative disorders and the myelodysplastic syndrome. Blood 2005 28 [Epub ahead of print].