

## Myeloproliferative Neoplasms – Classification, Diagnostic and Therapeutic Options in the Light of Molecular Findings

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### Abstract

The discovery of specific molecular aberrations (gene fusions or mutations) has had a profound effect on the understanding and management of myeloproliferative disorders (MPDs). First, it has provided clear evidence that all of these disorders are of neoplastic origin. This fact resulted in the change of the nomenclature proposed in the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues 2008, where the term MPDs was replaced by myeloproliferative neoplasms (MPNs). Second, useful tools for diagnostic procedures were developed, i.e. polymerase chain reaction (PCR) or other molecular assays. Thanks to this, previous complicated diagnostic algorithms could be simplified and the numerical value requirements could be lowered, making the diagnosis simpler and quicker. The other implication of the molecular findings in myeloproliferative neoplasms is derived from the fact that all discovered mutations result in translation of proteins with tyrosine kinase activity. So, nowadays the majority of myeloproliferative neoplasms can be treated with target therapy using tyrosine kinase inhibitors.

### Keywords

Myeloproliferative neoplasms, gene mutations, classification, diagnostic criteria, target therapy, tyrosine kinase inhibitors

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The term myeloproliferative disorders (MPDs) was introduced by Demeshek in 1951.<sup>1</sup> He postulated that various clinical conditions, such as chronic granulocytic leukaemia, polycythaemia vera (PV), idiopathic myeloid metaplasia, thrombocythaemia, megacariocytic leukaemia and erythroleukaemia, can be regarded as variable manifestations of proliferative activity of bone marrow cells. In the following few years, the term MPD was limited to forms of disease in which maturation of cells is preserved and – in contrast to acute leukaemias – the natural course is usually characterised by benign onset. Finally, four diseases – chronic myelogenous leukaemia (CML), PV, essential thrombocythaemia (ET) and myelofibrosis (MF) – were recognised as classic MPDs. In 1968, Hardy and Anderson introduced the term ‘hypereosinophilic syndrome’ (HES),<sup>2</sup> for which Chusid et al. proposed more defined criteria.<sup>3</sup> HES was regarded by some authors as a fifth form of MPD.

Originally, Demeshek assumed that these disorders and their different clinical manifestations resulted from the action of undiscovered myelostimulatory factors or mechanisms. Twenty-seven years later, Adamson and Fialkow postulated that the carcinogenic mutation of multipotential stem cells is the underlying cause of MPD.<sup>4</sup> The discovery of the Philadelphia chromosome (Ph) as a constant cytogenetic aberration in CML, the 6-phospho gluconate dehydrogenase (6-GPD) isoenzyme studies in heterozygous females with PV and ET started by Fialkow in 1974 and the clonogenic assay introduced by Bradley and Metcalf confirmed the hypothesis of the clonal nature of MPDs also in cases of hypereosinophilic syndrome.<sup>5</sup>

These factors were manifested in the 2001 edition of the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues, in which all of the disorders mentioned above were included in a chapter entitled ‘Myeloproliferative Diseases’.<sup>6</sup> At that time the term neoplasm was not used because there was a lack of solid criteria that in every case permitted the distinction of reactive from neoplastic proliferation. This is best illustrated by the fact that in the case of chronic eosinophilic leukaemia (CEL) the term hypereosinophilic syndrome was preserved. Mastocytosis was presented in this classification as a different entity, where cutaneous, usually benign, mastocytosis was put together with systemic forms of the disease.

The development and achievements of molecular biology in the last 25 years have confirmed the concept of the neoplastic nature of these diseases. In almost all of the mentioned disorders, specific molecular markers were found in the form of either gene mutations or gene fusions. In 1984, the *BCR/ABL* fusion gene, the result of a translocation between the 9 and 22 chromosomes, in 1993, the *KIT* gene mutation characteristic of systemic mastocytosis and in 2003, the *FLIP1L1/PDGFR* fusion gene characteristic for CEL were described.<sup>7,8,9</sup> Two years later, the *JAK2* gene mutation, found in the majority of PV cases and at least half of ET and MF cases, was uncovered.<sup>10-12</sup> All of the mentioned mutations result in translation of proteins with tyrosine kinase activity. They are responsible for constitutive activations of molecular pathways, leading to uncontrolled cell proliferation in MPDs. So, although these mutations have proved the neoplastic origin of MPDs, in some ways they are in accordance with Dameshek’s concept of dysregulation of myelopoiesis.

Following molecular findings, the most recent edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, issued in 2008,<sup>13</sup> has named these disorders as myeloproliferative neoplasms (MPNs), including mastocytosis, taking into account the origin of the mast cells. This change was based on strong evidence in terms of clonal mutations that confirmed that the neoplastic character of haematopoiesis is responsible for the pathogenesis of the vast majority of diseases from this group. A well-described molecular marker confirming the diagnosis can be found in most MPNs. The presence of the *BCR-ABL* fusion gene is a *sine qua non* condition for the diagnosis of CML; mutation of the *JAK2* (either *JAK V617F* in exon

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14 or mutation, deletion and insertion in exon 12) gene<sup>14</sup> can be found in more than 95% of patients with PV; and mutation at codon 816 (*D816V*) of the *KIT* gene is identified in the mast cells of 95% of adults with systemic mastocytosis. In ET and MF, the characteristic mutation of *JAK2* and *MPL* genes can be found in about 50–60% of patients.<sup>14,15</sup>

It is possible that there is only one *JAK2/MPL* disorder with various clinical manifestations (TE-like, PV-like, MF-like), which may depend on host genetic variations,<sup>16</sup> cells targeted by *JAK2/MPL* mutation,<sup>17</sup> level of *JAK2* kinase activity<sup>18</sup> or additional molecular events.<sup>19,20</sup>

In the new WHO classification, CEL is included in the MPNs, but only as the entity without molecular marker (not otherwise specified [NOS]). In our opinion, it was not advisable to drop the well-defined *FLI1L1-PDGFR* fusion gene from MPNs. Although there were some reasons to combine myeloid and lymphoid neoplasms with eosinophilia and abnormalities of the *PDGFRA*, *PDGFRB* and *FGFR1* genes into one category, from a historical and practical point of view the exclusion of CEL with *FLI1L1-PDGFR* fusion gene from the group of well-defined MPNs is a little anachronistic. The recent WHO classification yielded changes in the diagnostic criteria of MPNs. Currently, the criteria are based on molecular markers and accentuate the value of histopathological examination and verify the usefulness of some earlier clinical and laboratory parameters.

Although the diagnostic criteria of CML were not essentially modified, some interesting problems are discussed in the new proposal. The first one is the presence of monocytosis in rare cases of CML with p190 *BCR/ABL1* isoform, which can be the reason for a faulty diagnosis of chronic myelomonocytic leukaemia. The next problem is focal infiltration of bone marrow in the initial period of the blast crisis. This phenomenon leads to the necessity for a histopathological assessment of bone marrow due to the suspicion of a blast crisis, even when cytological examination does not show characteristic changes for this phase of disease.

The diagnostic criteria for the last three classic MPN were significantly changed. For PV, there are only two major criteria, with the obligatory

presence of the *JAK2* gene mutation. The other major criterion is verified concentration of haemoglobin needed for confirmation of diagnosis (>16.5 and >18.5g/dl for women and men, respectively). However, a haemoglobin concentration >15 and >17g/dl for women and men, respectively, can be regarded as diagnostic if associated with a documented and sustained increase of at least 2g/dl from an individual's baseline. Such modification allows earlier diagnosis than was possible previously. It is worth noting that irrespective of time, low erythropoietin (one of the minor criteria) is still of diagnostic value, in contrast to splenomegaly.<sup>21</sup> The next two minor criteria are dedicated to changes in bone marrow histopathological examination and assessment of erythroid colony growth *in vitro*.

Essential changes have been introduced to the diagnostic criteria of ET. The threshold value of a platelet count needed for the diagnosis is lowered to 450G/l. The fourth criterion is the presence of mutation of the *JAK2* gene or other clonal mutation (e.g. mutation of the *MPL* gene). Regrettably, in spite of the progress in molecular studies, the diagnosis of ET is essentially based on exclusion of secondary causes of thrombocytosis.

According to the current WHO classification, the histological bone marrow biopsy that reveals proliferation and atypia of megakaryocytes, accompanied by fibrosis, is the main diagnostic criterion for MF. The second criterion is *JAK2* or *MPL* gene mutation and, in its absence, exclusion of *BCR/ABL* mutation. A definitive diagnosis of MF requires the fulfilment of at least two of the four minor criteria: presence of leukoerythroblastosis in peripheral blood, increased serum lactate dehydrogenase level, anaemia and splenomegaly.

Persistent eosinophilia  $\geq 1.5G/l$  is fundamental for the diagnosis of CEL NOS. To make the diagnosis of CEL NOS, clonal cytogenetic or molecular abnormalities should be confirmed. As we mentioned, in

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our opinion the *FIP1L1-PDGFR* fusion gene should also be included. If no clonal marker is present, blast cells should be >2% in peripheral blood or >5% in bone marrow.

In terms of the possible treatment options, three subgroups of MPN can be discussed. The first are those diseases in which targeted therapy was shown to be successful. The second subgroup combines diseases in which the clinical effect of therapy directed to specific molecular marker still awaits confirmation. The third subgroup is aggregating diseases in which target therapy is not yet established.

CML is the most representative disease for the first subgroup. The treatment strategy for this disease has definitively changed over the last 10 years. The validation of the effectiveness of imatinib, the *BCR-ABL* kinase inhibitor, was the milestone in CML therapy. The introduction of imatinib to the therapy of CML made it possible to

achieve after 12 months of treatment complete haematological remission in 90%, complete cytogenetic response in 70–80% and major molecular response in 40% of patients in the chronic phase of this disease.

Although initial enthusiasm was dampened by long-term observation, nothing can deny the fact that oral, patient-friendly and low-intensity adverse-effect-causing therapy improved the life expectancy of CML patients, even compared with bone marrow transplantation. This conclusion was the basis for profound changes in standard therapy to imatinib as a first-line treatment in nearly all patients. However, long-term observations revealed that molecular remission is not obtained in 20–30% of patients even after 60 months of treatment, and it is lost in time by some patients.

The patients having no benefits of target therapy with imatinib became a group of special interest for clinical studies with imatinib. Long-term observations showed that the time to the consecutive phase of response varies among patients. This finding resulted in optimisation of the treatment time needed to achieve the next phase of clinical response.<sup>22</sup> The studies in the group of patients with late molecular response as well as in those who lost molecular response created the necessity for defining laboratory methods and therapy-monitoring standards.<sup>23</sup>

The next milestone in CML therapy was the discovery of mutations in the kinase *BCR-ABL* gene domain responsible for acquired imatinib resistance<sup>24</sup> and the development of *BCR-ABL* kinase inhibitors that were compatible with these mutations. Two of these inhibitors, dasatinib and nilotinib, were successfully validated in clinical studies and approved for clinical use as a second-line therapy.

Both mastocytosis and *FIP1L1-PDGFR*A-positive CEL included by the authors in the MPN group can also be included in diseases in which target therapy can be applied. Mutation *D816V* of the *KIT* gene results in ligand-independent activation of *KIT* kinase and provides resistance to imatinib.<sup>25</sup> In these cases, dasatinib appeared to be an effective drug.<sup>26</sup> However, activating point mutations in other codons of the *KIT* gene may be sensitive to imatinib. In our unpublished data, we have evidence of achieving a good response<sup>23</sup> in patients with SM and codon

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502–503 duplication of the the *KIT* gene mutation, which was previously described in patients with gastrointestinal stromal tumours (GIST).<sup>27</sup> Low doses of imatinib could also be used in patients with CEL and *FIP1L1-PDGFR*A mutation with excellent therapeutic effects,<sup>28</sup> even compared with results of bone marrow transplantation.<sup>29</sup>

As mentioned above, the second group of MPNs is composed of diseases with somatic mutations that constitutively activate *JAK2* signal transduction. This fact provides for the development of novel target

therapy for *JAK2*-positive patients with ET, PV and MF. These clinical studies are currently in phase I and II. The most advanced studies involve the ICNB018424 compound, a selective *JAK2* inhibitor. The first promising results of phase I and I/II studies were published in 2008.<sup>30</sup>

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The studies concerned patients with primary MF (independently of *JAK2* status) and *JAK2*-positive post-PV/ET myelofibrosis. Administered orally, ICNB018424 invokes a clinical response, including improvement of the general condition of the patient, reduction of splenomegaly and diminishing constitutional symptoms; however, it was also responsible for thrombocytopenia, especially when given at higher doses.

In the pre-clinical phase of studies there are other selective inhibitors (TG101209 and TG101348). Compounds identified as other mutation inhibitors showing activity towards *JAK2* are still awaiting clinical assessment. Due to the good prognosis, long-term survival expectancy and the so far unclear prognostic value of *JAK2* mutation, the use of ICNB018424 and other inhibitors in patients with PV and ET needs detailed description of the safety profile. Due to the central role of *JAK2* signalling in several cellular processes, there is apprehension about toxicity associated with wide *JAK2* inhibition and 'off-target' inhibition of *JAK1*, *JAK3* and *TYK2*.

The therapy for the third group, i.e. no molecular target disease, is based on the *primum non nocere* rule. Clinical decisions are based on increasingly precise assessment of the risk factors of thrombotic/haemorrhagic complications and the risk of progression to the fibrotic phase or blast transformation as well. The appraisal of the risk of blast transformation is complicated by the fact that long-term use of cytostatics is responsible for increased risk of disease transformation. Although there was no direct evidence, this was the reason for abandoning myleran therapy in ET patients.

The risk of complications in PV and ET was studied by some authors. Thrombotic history and age >60 years in both PV and ET seem to be incontestable factors. The importance of cardiovascular risk factors is still unclear. The latest reports show that leukocytosis can be regarded as a risk factor for complications as well as blast transformation.<sup>31</sup> The recognition of these risk factors needs further study; moreover, the platelet count seems not to be prognostic. The high risk of bleeding in patients with extremely high platelet counts (>1,000G/l) is currently regarded as a phenomenon related to acquired von Willebrand disease.<sup>32</sup> The presence of any known risk factors classifies the patient into the high-risk group.

In the case of PV, patients usually undergo phlebotomies and are put on low-dose aspirin. When patients are in the high-risk group, therapy with hydroxyurea (HU) is started. When intolerance or resistance to HU occurs, it is permitted to use interferon- $\alpha$ , pipobroman or myleran as a second-line therapy.

With the exception of phlebotomy, the same treatment regime is used for ET. So far, there is no clear evidence of the supremacy of anagrelide over HU treatment. Due to the cardiac complications, anagrelide cannot be regarded as first-line therapy, especially in elderly patients. In young patients from the high-risk group, especially those who are *JAK2*-negative, the non-cytostatic character of anagrelide can be the reason for the choice of this drug as an up-front therapy.

A slightly different therapeutic approach is taken in the case of MF patients. As MF has a definitively worse prognosis than PV and ET, one should consider the idea of bone marrow transplantation as a therapeutic approach. A recently published prognostic model by the International Working Group for Myelofibrosis Research and Treatment more precisely indicates the candidates who can profit from bone marrow transplantation.<sup>33</sup> Age >65 years, the presence of general symptoms, haemoglobin level <10g/dl, leukocytosis >25G/l and presence of blast >1% in peripheral blood are recognised as unfavourable prognostic factors. A bad prognosis is also the reason for seeking new therapeutic options. As discussed above, *JAK2* inhibitors, clinical studies on angiogenesis, signal transduction and proteasome and histone deacetylase inhibitors are currently under development.<sup>34</sup> These trials are in the early pre-clinical phase and some promising results have been reported.

Considering the developments in molecular biology in the few last years and recent proteomics studies, one could also expect that in the near future a specific molecular marker will be found for all

patients with a diagnosis of myeloproliferative neoplasms, and the relevant target therapy administered. ■



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