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MPD VOICE

Voice of the Myeloproliferative Disorders Community

doctor-patient sharing

JAK 2 ISSUE

INSIDE:

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President's Note

Joyce Niblack

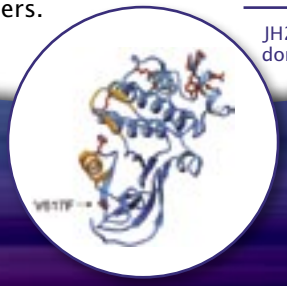
The first issue of the MPD VOICE was going to focus on the recent February 25-27, 2005 Patient conference sponsored by the Mayo Clinic Comprehensive Cancer Center and the CMPD Education Foundation. However, the stunning news of the discovery of the JAK2 tyrosine kinase mutation found in philadelphia chromosome-negative MPD patients (ET, PV and MMM) trumped everything.

The face of CML treatment was changed by the discovery of Gleevec which targets the bcr-abl tyrosine kinase responsible for that disease. Gleevec also targets the c-kit tyrosine kinase involved in GIST (gastrointestinal stromal tumor) and has given hope where there was none before. Now we stand on the brink of our own targeted therapies and better diagnostic tools. Work is already in progress for finding a drug or drugs that inhibit the JAK2 tyrosine kinase mutation and just a matter of time before we have our own Gleevec counterparts. While several other groups have also published on this discovery, we owe a very special thanks to Gary Gilliland, MD and his colleagues, particularly Martha Wadleigh, MD and Stephanie Lee, MD who were primary in organizing the study announced on mpd-net to accrue patients for their study that yielded results based on the study of blood and DNA samples from 345 on-line participants. Dr. Gilliland accepted my invitation to the speakers of the 2003 Mayo patient conference to use our large on-line mpd community for their studies. I hope more of you will participate in future studies announced on mpd-net.

Dr, Gilliland and his colleagues want to make sure that those who didn't participate in the study but would like to be included, know that they can still do so. If you are interested, full information about the study and how to apply are at www.mpdinfo.org under mpd-net. There is a link on the first page of the mpd-net section. Or, email Dr. Martha Wadleigh at MWadleigh@partners.org – include your diagnosis (only PV, ET, MF/AMM/MMM) as well as your name and mailing address.

The Harvard group just asked me to announce another study directed at CML patients. This study is for people with newly diagnosed CML (within one year of dx), and is similar in that pts complete surveys, donate blood samples and provide medical records. People are followed every 6 months. All interested in participating, can contact Tarrah Kirkpatrick, MS, Project Manager. Harvard CML & MPD Studies, Dana-Farber Cancer Institute Toll Free: 866-HAVE-CML (1-866-428-3265) Email: HarvardCML@dfci.harvard.edu www.HarvardCMLStudy.org

In this first issue, we have articles by Drs. Ayalew Tefferi and Gary Gilliland. The first is a general overview of Chronic Myeloproliferative Disorders. The second explains the significance of the JAK2 connection to philadelphia chromosome negative chronic myeloproliferative disorders.



JH2 (pseudokinase) domain JAK2 model

1. Mayo Clinic, Scottsdale, Arizona
2. Fred Hutchinson Cancer Research Center, Seattle, Washington
3. Harvard Institutes of Medicine, Boston, Massachusetts
4. Mayo Clinic, Rochester, Minnesota
5. Mayo Clinic, Rochester, Minnesota
6. MD Anderson Cancer Center, Houston, Texas

Myeloproliferative Disorders:

What They Are And How They Are Classified

Ayalew Tefferi and D. Gary Gilliland
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Myeloproliferative disorders (MPD) represent a class of hematological malignancies that are characterized by an abnormal accumulation in the peripheral blood and bone marrow, of mature appearing myeloid cells (e.g. granulocytes, red blood cells, platelets) as well as their precursors (e.g. myelocytes, metamyelocytes, nucleated red blood cells, megakaryocytes). The cause of this abnormal myeloproliferation is an acquired (i.e. generally not hereditary) genetic mutation that affects a hematopoietic stem cell. Therefore, the MPD are sometimes referred to as clonal stem cell disorders. In addition to producing leukocytosis, thrombocytosis, and/or erythrocytosis, clonal myeloproliferation in MPDs might also disturb the bone marrow microenvironment resulting in the formation of collagen fibrosis (myelofibrosis), new blood vessels (angiogenesis), and new bone (osteosclerosis). This bone marrow stromal reaction is believed to be mediated by cytokines that are abnormally released by megakaryocytes. Such cytokines are also believed to be responsible for abnormal blood cell formation in the spleen and liver (i.e. extramedullary hematopoiesis) that usually accompanies some forms of myeloproliferative disorders.

The term "MPD" was first introduced by Dr. William Dameshek, a prominent hematologist of his time, in recognition of the clinical and bone marrow histological similarities between essential thrombocythemia (ET; also known as primary thrombocytosis), pol cythemia vera (PV; also known as polycythemia rubra vera), myelofibrosis with myeloid metaplasia (MMM), and chronic myeloid leukemia (CML)[1]. MMM can either present *de novo* (i.e. without prior history of either PV or ET) or develop from both ET and PV. *De novo* MMM is referred to as either agnogenic myeloid metaplasia (AMM) or chronic idiopathic myelofibrosis. MMM developing from ET is called post thrombocythemic myeloid metaplasia (PTMMM) and that from PV post polycythemic myeloid metaplasia (PPMMM).

The aforementioned four disorders (PV, ET, MMM, CML) constitute the 'classic' or Dameshek's MPD and should be distinguished from other chronic myeloid disorders including 'atypical' MPD and the myelodysplastic syndrome (MDS) (*table 1*). The atypical MPD category includes chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), hypereosinophilic syndrome (HES), chronic basophilic leukemia (CBL), systemic mastocytosis (SM), and unclassified MPD (UMPD). Each of these clinicopathologic entities has its own diagnostic criteria that are different from those of the classic MPD. MDS is considered separate from both classic and atypical MPD and its diagnosis requires the demonstration of dysplastic morphological features that involve red cell and other myeloid precursor cells. Also, MDS has a higher propensity to transform to acute myeloid leukemia (AML) when compared with both classic and atypical MPD. Among the classic MPD, the disease-causing mutation is known only for CML[2]. Accordingly, the presence of this particular mutation, known as the Philadelphia translocation (*Bcr/Abl*), distinguishes CML from the *Bcr/Abl*-negative classic MPD (ET, PV, MM) (Table 1).

Table 1

Modern Classification of Chronic Myeloid Disorders

1) Classic Myeloproliferative disorders

a. *Bcr/Abl*-positive
   i. Chronic myeloid leukemia

b. *Bcr/Abl*-negative
   i. Essential Thrombocythemia
   ii. Polycytheniia Vera
   iii. Myelofibrosis with Myelold Metaplasia

2) Atypical Myeloproliferative Disorders

a. Molecularly-defined
   i. PDGFRA-rearranged Eosinophlic/Mast Cell Disorders
   ii. PDGFRB-rearranged Eosinophlic Disorders
   iii. Systemic Mastocytosis Associated with *c-kit* Mutation
   iv. *8p11* Myeloproliferative Syndrome
   v. Juvenile Myelomonocytic Leukemia with Recurrent Mutations of RAS Signaling Pathway Molecules

b. Clinicopathologically-Assigned
   i. Chronic Neutrophilic Leukemia
   ii. Chronic Eosinophilic Leukemia, Molecularly Not Defined
   iii. Hypereosinophlic Syndrome
   iv. Chronic Basophilic Leukemia
   v. Chronic myelomonocytic Leukemia
   vi. Systemic Mastocytosis, Molecularly Not Defined
   vii. Unclassified Myeloproliferative Disorder

3) Myelodysplastic Syndrome

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JAK2V617F: A New Mutation in Myeloproliferative Disorders Offers Hope for the Development of Effective Treatment Agents

(The following article is based on an upcoming paper in the July issue of *The Mayo Clinic Proceedings*, by permission.)

Ayalew Tefferi and D. Gary Gilliland
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Polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis with myeloid metaplasia (MMM), and chronic myeloid leukemia (CML) constitute the classic myeloproliferative disorders (MPD).[1] Over the last 40 years, a large amount of laboratory work has clearly established the classic MPD as clonal stem cell diseases.[2] To date, however, the specific disease-causing mutation has been identified only for CML.[3] In this instance, the particular mutation, known as the Philadelphia translocation, transforms the normal Abl tyrosine kinase into a cancer-causing tyrosine kinase called Bcr/Abl. Over the last 3 months, a new mutation affecting another tyrosine kinase, the Janus tyrosine kinase-2 (JAK2) has been identified in a substantial proportion of patients with PV, ET, or MMM but also infrequently in other chronic myeloid disorders.[4-10] Furthermore, the particular mutation (JAK2^{V617F}) has been shown to cause increased hematocrit in mice that is reminiscent of PV in humans.[5] This new discovery will hopefully lead towards the development of small molecule kinase inhibitors for patients with MPD as has been the case with CML and imatinib mesylate (Gleevec™).[11]

What are protein kinases and what is JAK2?

Protein kinases (PK) are enzymes that catalyze the addition of a phosphate molecule onto other proteins (i.e. protein phosphorylation). Such action is essential for transfer of message from the cell wall to the nucleus (i.e. signal transduction). There are more than 500 PK in the cell and among them is a subclass, protein tyrosine kinases (PTK), that catalyze the transfer of a phosphate group from ATP to specific tyrosine residues in signal transduction molecules. There are two categories of PTK; receptor protein-tyrosine kinases (RPTK) and cytoplasmic protein-tyrosine kinases (CPTK).[12,13] In humans, there are approximately 90 known PTK genes; 58 encode for RPTK and 32 for CPTK.[14] Examples of MPD-pertinent RPTK include platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (Kit), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and fms-related tyrosine kinase 3 (Flt3). Examples of CPTK include the Janus family of kinases (JAK1, JAK2, JAK3, TYK2), the Src family of kinases (homologues of the Rous sarcoma virus oncoprotein), and Abl kinase (homologue of the Abelson murine leukemia virus oncoprotein).

JAK2 (Janus kinase 2) is a cytoplasmic protein-tyrosine kinase and its structure is uniquely characterized by the presence of two homologous kinase domains; JAK homology 1 (JH1) that is functional (i.e. has the kinase enzymatic activity) and JH2 that lacks kinase activity (i.e. it is a pseudo-kinase). JAK2 receives signals from the cell wall when specific cytokine receptors are engaged with various cytokines including erythropoietin (Epo), interferons, interleukins, and growth factors. Such cytokine-cytokine receptor binding is required to normally activate JAK2, which in turn activates other signal transduction molecules by facilitating their phosphorylation. When JAK2 is mutated, it spontaneously activates itself resulting in sustained (i.e. unregulated) message transfer to the nucleus where genes that cause cancer are continuously stimulated to be expressed. The message from JAK2 to the nucleus is transferred through other signal transduction molecules called signal transducers and activators of transcription (STATs). This JAK/STAT signal transduction pathway plays a major role in both cellular proliferation and cell survival.

The JAK2^{V617F} Mutation and Myeloproliferative Disorders

The JAK2 gene is located on the short arm of chromosome 9 and specifically at a region referred to as 9p24. Interestingly, the same chromosomal region has been a frequent site of either a gross or submicroscopic structural chromosome abnormality that is frequently seen in PV and MMM. Furthermore, other studies have long implicated the JAK/STAT pathway in the pathogenesis of MPD. Therefore, it was reasonable to pursue JAK2 mutation studies in PV, ET, and MMM.

To date, seven independent studies have described an association between a particular JAK2 mutation (JAK2^{V617F}) and MPD.[4-10] In the first study from the US (led by Dr. Gilliland), the mutation was detected in 121 of 164 patients with PV (74%; homozygous in 25%), 37 of 115 patients with ET (32%; homozygous in 3%), and 16 of 46 patients with MMM (35%; homozygous in 9%).[7] Buccal smear analysis confirmed that JAK2^{V617F} was an acquired and not a hereditary condition. Similarly, the mutation was not detected in 270 control subjects. This study did not reveal clinical differences between patients with the mutation and those without.

The second study from the UK (led by Dr. Green) detected the mutation in 53 of 73 patients with PV (73%; homozygous in 26%), 6 of 51 with ET (12%; homozygous in 0%), and 7 of 16 with MMM (44%; homozygous in 19%). However, when the authors utilized a more sensitive technique (i.e. allele-specific PCR), the detection rates increased to 97% in PV, 57% in ET, and 50% in MMM. Although restricted by small sample size, the presence of the mutant allele in patients with either ET or MMM did not confer a different clinical course.

The third study from France (led by Dr. Vainchenker) disclosed mutation incidences of 89%, 43%, 43%, and 0% in PV (n=45), ET (n=21), MMM (n=7), and secondary erythrocytosis (n=35), respectively.[5] Furthermore, the authors were able to show both JAK2^{V617F}-mediated Epo-hyper-

sensitivity in cell lines and increased hematocrit in mice whose bone marrow stem cells were infected with the particular mutation.

In the fourth study from Switzerland and Italy (led by Dr. Skoda), the JAK2^{V617F} mutation was detected in 83 of 128 patients with PV (65%; homozygous in 27%), 21 of 93 with ET (23%; homozygous in 3%), 13 of 23 with MMM (57%; homozygous in 22%), and 0 of 11 with secondary erythrocytosis. Similar to the case in all the other 3 studies, the specific mutation was not detected in healthy individuals. Also in this study, the authors were able to demonstrate JAK2^{V617F}-mediated growth factor hypersensitivity as well as enhanced STAT5 phosphorylation in cell lines. In addition, the particular study suggested a higher incidence of myelofibrosis, hemorrhage, and thrombosis in patients with the mutations as opposed to those without.

In the fifth study from the US (led by Dr. Zhao),[9] JAK2^{V617F} was detected the in either peripheral blood mononuclear cells or purified erythroid colony-forming cells from 20 of 24 patients (83%) with PV but in none of 12 controls.

In the sixth study from the US (led by Dr. Tefferi), involving over 240 patients, revealed the infrequent (0-25%) but definite occurrence of the JAK2^{V617F} mutation in other chronic myeloid disorders including chronic myelomonocytic leukemia (3%), myelodysplastic syndrome (5%), chronic neutrophilic leukemia (17%), and systemic mastocytosis (25%).[8]

Finally, in the seventh study (led by Dr. Cross), a collaborative effort between investigators in the UK, Greece, Germany, and the US, looked at the incidence of JAK2^{V617F} in both the classic bcr/abl-negative MPD (i.e. PV, ET, MMM) and the atypical MPD.10 JAK2^{V617F} was detected in 13 of 53 patients with UMPD (25%), 17 of 99 patients with either CMML or CML-like UMPD (17%; 2 of 6 patients with CNL expressed the mutation), 2 of 127 patients with HES (2%), 0 of 7 cases with FIP1L1-PDGFRA+ eosinophilic/mast cell disorder (0%), 0 of 28 patients with SM (0%), 0 of 17 patients with AML (0%), 0 of 18 patients with CML (0%), 0 of 4 patients with secondary erythrocytosis (0%), and 0 0f 160 healthy controls (0%). This study also included 72 patients with PV, 59 with ET, and 35 with MMM with the respective JAK2^{V617F} mutational frequencies of 81%, 41%, and 43%, respectively.

Discussion and Clinical Implications

Based on the above information, the laboratory detection of JAK2^{V617F}, either in bone marrow or peripheral blood myeloid cells, is highly suggestive of a MPD as opposed to reactive myeloproliferation such as secondary erythrocytosis. However, it is clear that the presence or absence of JAK2^{V617F} can not distinguish among different MPD subgroups.

Additional studies are clearly needed to establish the most accurate laboratory assay that detects JAK2^{V617F} as well as the prevalence of the specific mutation in a larger cohort of patients with ET and MMM. Furthermore, it would be interesting to see if there is a difference in the incidence of the mutation between AMM, PPMM, and PTMM. Such work is currently being performed by our group and will be communicated soon.

Future studies of pathogenesis of JAK2^{V617F}-negative MPD will no doubt focus on possible abnormalities of either other JAK/STAT pathway molecules or their regulatory elements. Similarly, additional studies are needed to clarify if the JAK2^{V617F} mutation by itself is sufficient enough to cause a MPD and what other mutational events are responsible for the difference in clinical features among PV, ET, and MMM despite their common link with the particular mutation. From a therapeutic standpoint, one can envision targeting JAK2 directly or its downstream effectors. In this regard, several lead compounds, such as AG-490, have already been identified and it is only a matter of time before clinical trials involving small molecule JAK2 inhibitors are developed.

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CMPD Education Foundation

Joyce Niblack

The CMPD Education Foundation, a 501 (c)(3) non-profit organization, was incorporated in early 1994 at the urging of Dr. Ayalew Tefferi of Mayo Clinic (Rochester, MN). Some months before the Mayo 2003 patient conference, Dr. Tefferi started urging me to form a patient- based foundation to make it easier to raise funds for further patient conferences and development of educational materials. I already had a full plate, didn't think I could do anymore at the time and sat on the idea. But dedicated person that he is, at the 2003 Conference, Dr. Tefferi expressed his belief that we needed a patient-based non-profit foundation to fulfill this role. The attendees were in favor of this and CMPD Education Foundation was born. We all should be grateful to Dr. Tefferi for his dedication to MPD patients, his efforts to make sure we have the very best experts on the speakers' panel for the Mayo Clinic Comprehensive Cancer Center (which embraces Rochester, Scottsdale and Jacksonville)/ CMPD Education Foundation Patient conferences. While conferences were originally scheduled every two years, the JAK2 discovery and ongoing work on finding targeted therapies led Dr. Camoriano (Mayo Scottsdale, AZ) to suggest that we move up the date for the next conference to fall of 1996. So look for coming announcements on mpd-net and in future newsletters.

Those of you who attended the February 25-27,2005 Mayo/CMPD Education Foundation Scottsdale Conference probably noticed the speakers clustering at every opportunity. One of the outgrowths of the JAK2 finding is a strengthening of the collaborative efforts among these top MPD experts/ researchers. As a result, Dr. Tefferi's vision has expanded for our organization to the following network to further the search for a cure:

- Information, education and support
- Patient and MD conferences
- Doctor-patient sharing
- Doctor/Doctor/Researcher networking
- MPD community support for both education and research.

Our new director, Rob Leary and I have been kicking around ideas for fund raising to support the above goals. Our first priority, at Dr. Tefferi's urging, will be fund raising efforts to support further JAK2 and related pre-clinical research for better therapies and potentially a cure for our diseases. The lion's share of research and development costs for targeted therapies will have to be born by the major pharmaceutical companies who undertake drug development and approval for better therapies for us. But the MPD Community can and should do everything we can to raise funds to support the pre-clinical and other testing and DNA screening for further targets, more sensitive tests to identify who will benefit from the targeted therapies that will be developed, additional molecular targets, etc. If you wish donations to go to the Eileen Schabel memorial JAK2 research fund established by her widower mark your checks JAK2 research. We look forward to working with all of you to meet the above goals.

CMPD Education Foundation members automatically are on the newsletter mailing list. Those who requested a newsletter but are not members will receive a complimentary copy. To continue receiving future issues, we have enclosed a membership application for your convenience.

MPD-NET Online Support Group

Joyce Niblack

As I mentioned in the President's Note, Dr. Gilliland's group accrued patients through mpd-net, an online support group with over 2200 members. The announcement was mirrored on our associated website www.mpdinfo.org.

There are 4 active members of the mpd-net management team: Joyce Niblack, founder and team leader;

Ian Sweet; Lyn Burns; and Bob Pasker. Larry Milnes retired from active participation in daily duties, but as our emeritus list manager, fills in as needed. Larry continues to maintain the mpd md list he started developing before he joining the list management team and continues to help mpd-net members looking for a doctor in their area or with contact information for one of the experts. You can contact Larry at LarryMilnes@comcast.net.

To join mpd-net, send an email to mpd-net-request@listserv.acor.org with your first and last name and diagnosis. You will receive two welcome letters after you are subscribed to the list explaining how things work and how to post to the list.

There is a wealth of information in the searchable mpd-net archives which are accessible only by members. Basic information on our diseases can be found in the FAQ files at www.mpdinfo.org which are being updated and expanded.

Membership Application

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- ❑ Agnogenic Myeloid Metaplasia (AMM aka MF, IMF, MMM)
- ❑ Essential thrombocythemia (ET)
- ❑ Polycythemia Vera (PV)
- ❑ MF Secondary to ET or PV
- ❑ Chronic Myelogenous Leukemia (CML)
- ❑ Mastocytosis
- ❑ Eosinophilic Syndrome/leukemia
- ❑ Chronic monomyelocytic leukemia (CMML)
- ❑ Myelodysplastic Syndrome (MDS)

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