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MPD VOICE

Voice of the Myeloproliferative Disorders Community

Patient-Doctor Sharing

JAK2 Inhibitor Clinical Trials

INSIDE:

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From the President

Joyce Niblack

John Camoriano, MD and Joyce at February 2007 Conference

At the February 23-25, 2007 Mayo/CMPD Education Foundation MPD conference, Dr. Tefferi told us there would be 5 JAK2 mutation inhibitors in clinical trials over the nex 12 months. This was dynamite news! The JAK2 mutation which affects most PV patients and about half of ET and MF patients, was only published in early 2005. There are high hopes that therapies targeting this and related mutations since identified will change the face of treatment for myeloproliferative disorders as Gleevec did for CML.

This issue was going to focus on highlights of the 2007 conference, but with the opening of multiple clinical trials since February, we are changing focus. Drs. Tefferi, Gilliland and Verstovsek of Mayo, Harvard and MD Anderson and their colleagues are working hard with the pharmaceutical companies to bring these new therapies to patients as quickly as possible. They have been kind enough to contribute an article summarizing their progress.

As trials open, they are listing on the clinical trial page of www.mpdinfo.org The class of drug, route of administration, manufacturer, clinical trial sites and clinical investigators and criteria are all there for you. We welcome trial participants to share their experiences on mpd-net.

The conference summaries run 29 pages so rather than trying to handle these via newsletter, they have been placed in a new section of www.mpdinfo.org

The other big news is the cooperative agreement reached between CMPD Education Foundation and MPD Foundation. More about that later in this newsletter.

Novel Mutations in Myeloproliferative Neoplasms and the Promise of Targeted Therapy

Ayalew Tefferi, Animesh Pardanani, Srdan Verstovsek, Ross Levine, Hagop Kantarjian, D. Gary Gilliland
Mayo Clinic, Harvard, and MD Anderson Cancer Center

We have come a long way, in terms of the molecular pathogenesis and treatment of myeloproliferative disorders (MPDs), since their first description by William Dameshek in 1951.[1] It all started with the 1960 discovery of the Philadelphia chromosome (an abnormally small chromosome 22) in chronic myelogenous leukemia (CML).[2] It took 30 years of intense laboratory research to first decipher the Philadelphia chromosome as a BCR-ABL mutation and then show its ability to induce CML-like disease in mice.[3]

(continued next page)

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

BCR-ABL is a leukemia-causing mutation of the intracellular enzyme called ABL, which is one of many tyrosine kinase enzymes in blood and other cells. In 1996, Brian Druker discovered imatinib, a small molecule drug that inhibits the activity of BCR-ABL and produces remissions in more than 90% of CML patients.[4] In 2003, imatinib was declared superior to conventional drug therapy in CML, based on a large randomized study, and long-term results now show an unprecedented ~ 87% 5-year survival in imatinib-treated patients.[5] The prospect of a similar success story in polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) was raised by a series of recent discoveries regarding the molecular pathogenesis of these disorders.

In early 2005, a novel mutation affecting another intracellular tyrosine kinase called JAK2 was discovered in PV, ET, and PMF and the mutation is currently identified as "JAK2-V617F".[6-9] In early 2007, another set of JAK2 mutations called "JAK2 exon 12 mutations" were described in patients with PV who are negative for JAK2-V617F.[10] Therefore, it now appears that almost all patients with PV carry either JAK2-V617F or JAK2 exon 12 mutations.[11] However, JAK2-V617F is also found in approximately 50% of patients with either ET or PMF.[12,13] In 2006, yet another mutation, this time affecting the cell membrane receptor for thrombopoietin (a cytokine that is the main growth factor for megakaryocytes and responsible for platelet production) was found in approximately 5% of patients with PMF and 1% with ET.[14,15] The thrombopoietin receptor is called MPL and the mutation MPL-W515L/K. All three mutation types have been shown to induce either a PV-like (JAK2-V617F and JAK2 exon 12 mutation) or PMF-like (MPL-W515L) disease in mice.[16]

All of the above-mentioned mutations originate in the hematopoietic stem cell and result in constitutive (i.e. cytokine-independent) activation of the JAK-STAT signal transduction pathway. The JAK-STAT pathway appears to be hyper-activated also in patients without any one of the aforementioned mutations. This suggests that JAK2 or MPL mutation-negative MPD patients harbor as yet unidentified mutation(s) that are functionally similar to those described above. Therefore, it is reasonable to consider the possibility that inhibition of the JAK-STAT pathway, via an anti-JAK2 drug, would benefit patients with PV, ET, or PMF, regardless of whether or not they carry known JAK2 or MPL mutations. In support of this contention, our preclinical studies have shown similar activity of JAK2 inhibitor drugs in mutation-positive and mutation-negative patients with PMF.[17]

Several pharmaceutical companies have already developed small molecule drugs that are potent inhibitors of JAK2.[18] For example, we have recently collaborated with scientists at TargeGen Inc. and reported on an oral drug that strongly inhibited JAK2 in cell lines with the relevant mutations and in patient-derived cells.[18] Because JAKs (Janus kinases), including JAK2, are physiologically important enzymes, a candidate JAK2 inhibitor drug should be as selective as possible and spare other tyrosine kinases including other JAKs such as JAK3, JAK1, and TYK2. In addition, candidate drugs are chosen based on their pharmacologic properties and animal toxicity profile. In general, orally bioavailable drugs that affect JAK2 much more than JAK3 have the most appeal.

From the standpoint of clinical trials that are either currently active or soon to be opened, two types of JAK2 inhibitors are being evaluated. The first involve drugs that were specifically developed with MPD patients in mind and with the intention to selectively inhibit JAK2. These include an oral drug from Incyte Inc. (patient accrual has already started at the MD Anderson Cancer Center and the study will soon open at the Mayo Clinic as well), another oral drug from Exelixis Inc. (scheduled to open in a few weeks at all three of our institutions as well as other additional sites), and the aforementioned oral drug from TargeGen Inc. (scheduled to open late this year at all three of our institutions and other additional sites). The second series of JAK2 inhibitors involves drugs that were developed for other malignancies, such as acute or chronic myeloid leukemias, with the intent to inhibit other enzymes, but were also found to inhibit JAK2. These include an oral drug from Cephalon Inc., which is a FLT3 inhibitor and two other intravenously administered drugs, from Merck Inc. and Astex therapeutics Ltd., that are potent inhibitors of the aurora kinases (all three drugs are currently being evaluated at MD Anderson Cancer Center). For more information, visit the MPD clinical trials web page at http://www.mpdinfo.org/).[19]

MDA Anderson has also just activated the Exelixis study on July 26 and the first patient began treatment the week of July 30.

Finally, the early phase studies using anti-JAK2 agents in MPDs will include high-risk PMF patients only because of lack of information regarding drug toxicity in humans and the fact that most patients with MPDs enjoy long-term survival with reasonably good quality of life. However, once drug safety and therapeutic activity is established, we anticipate that study eligibility criteria will be relaxed leading towards large scale randomized trials in both PV and ET. These are exciting times for the MPD community and the future looks bright for MPD patients whose courage, tenacity, involvement in patient education and advocacy, and financial support to accelerate scientific progress[19,20] is increasingly being recognized.[21]

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February 2007 MPD CONFERENCE NEWS

The February 23-25, 2007 Mayo/CMPD Education Foundation Conference was a great success. Dr. Tefferi broke the exciting news that 5 JAK2 inhibitors would enter clinical trials over the next 12 months. Dr. Verstovsek updated us on the status of Pegasys and oral interferon trials. Dr. Vardiman explained the new WHO (World Health Organization) diagnostic criteria for PV, ET and MF. Dr. Mesa discussed the findings of the Quality of Life Survey. A copy of the Mesa et al article that appeared in the November 2006 issue of Cancer and a newsletter summarizing the findings were included in conference materials. Many thanks to the 1197 patients from 30 countries and 6 continents who participated in the survey announced on mpd-net and www.mpdinfo.org for contributing to these important findings. Dr. Silver took us through PV diagnosis and treatment, Dr. Camoriano did a magnificent job of providing an overview of PV, ET and MF, Dr. Tallman spoke about options when MPDs convert to AML, Dr. Deeg updated us on transplantation in MPDs, Dr. Mesa stepped in for Dr. Nagorney and spoke about splenectomy in MPDs, Holly Bright, a Mayo Scottsdale exercise physiologist talked about exercise and led the audience through a series of stretching, strengthening and aerobi excersises in three sessions, and Joyce Niblack spoke about being your own advocate. A summary of the conference talks is on www.mpdinfo.org

Many thanks to our MD speakers and to Holly for devoting a weekend to meet with MPD patients and their families. Putting faces to names:

Front row left to right: Holly Bright, Joachim Deeg, MD, James Vardiman, MD, Gary Gilliland, MD, Srdan Verstovsek, MD Back row left to right: Lawrence Solberg, MD, Ayalew Tefferi, MD, Richard Silver, MD, Joyce Niblack, JD, John Camoriano, MD, Ruben Mesa, MD

The conference coordinators were (left to right), John Camoriano, Bob Niblack, Joyce Niblack, Ruben Mesa, Ayalew Tefferi (not shown)

Joachim Deeg, MD, Richard Silver, MD, Ayalew Tefferi, MD at the February 2007 conference

Pegylated and interferon clinical trials

Dr. Verstovsek summarized current therapies and clinical trials for mpds in his talk at the February 2007 MPD conference.

He discussed both PEG Intron and Pegasys, two different long acting dosage forms of interferon-alpha. His conclusion was PEG Intron is too toxic and similar to regular interferon. There were 42 patients in the study (21 with ET and 21 with PV). None had previously been on interferon. The dose was 0.5-1 mcg (microgram) weekly. The goal was normalization of blood counts (complete response, CR) The CR rate was 69% after 6 months of therapy. The majority of PV patients had a decrease in phlebotomies. After 2 years 55% stopped therapy due to toxicity.

Pegasys was studied in 32 PV patients who had not previously been on interferon-alpha. Most were JAK2 mutation positive. The dose was 90-180 mcg weekly. The goal was normalization of blood counts and elimination of splenomegaly (CR). After 12 months of therapy, 84% (27) of patients were in complete remission (CR), 3 patients in partial response (10%) and 2 patients had stopped therapy due to side effects. The percentage of cells in the blood with JAK2 mutation decreased in almost all patients.

Comparing PEG Intron vs Pegasys:

-PEG parts are chemically different
-PEG Intron is metabolized in the liver
-Pegasys is not-it is excreted by the kidneys
-Pegasys primarily stays in the blood circulation
-Since the blood volume is similar between patients, Pegasys is given as a uniform dose, not based on weight.

There was no response in the MD Anderson oral interferon trial. This pretty much parallels the older Mayo oral interferon trial results.

The Pegasys clinical trials for ET and PV are still open at MD Anderson. Check the clinical trial page on www.mpdinfo.org for details.

CMPD Education Foundation and MPD Foundation Cooperation

In June, Joyce and Bob Niblack of the CMPD Education Foundation and Barbara Van Husen of the MPD Foundation met in Rochester, Minnesota ro work out a cooperative agreement with their respective Foundations. Dr. Ayalew Tefferi of Mayo Rochester and the MPD Research Alliance joined the talks. The two foundations will be working together in a number of areas and will be supporting each others' efforts. A common goal is to insure that up-to-date information on surveys, studies, clinical trials, treatment options, etc are available to any mpd patient who has access to a computer. To that end, the foundations have linked to each other's websites and the CMPD Education Foundation has agreed to the MPD Foundation linking directly to our clinical trial page so that clinical trial information is easily available to patients regardless of which site they reach first. Joyce and Bob will be participating in future MPD Alliance meetings with the Board of MPD Foundation. There are other areas of cooperation. This is a very positive step.

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