MPN FOCUS

The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia Newsletter

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

November 2014

Trials, Tribulations, and Blessings

by Barbara W. Coleman

Since allowing God to come into my life, I have come to know well the terms FAITH, TRUST and BELIEF. They have guided me through the worst of times. My family and I have always been churchgoers. In the mid 1990's, I was diagnosed with polycythemia vera, a disease where the body produces too much blood. At the time, Dr. Edward Oleen at Phoebe Putney Memorial Hospital in Albany, Georgia was my doctor. He was a kind, soft-spoken, yet thorough physician who I learned to trust. He tried me on several medications until he discovered one that worked best for me. After years of assisting me, he recommended that I see a colleague of his (Dr. Elliott Winton) at Emory University Hospital in Atlanta, Georgia. Though Dr. Oleen was very knowledgeable, some of his findings, as pertained to me, were baffling. So, he sought help through Dr. Winton. It came as no surprise that Dr. Winton was also mild-tempered and thorough as Dr. Oleen. Both won my respect as practitioners in the area of Hematology/Oncology. Through Dr. Winton, I learned about the symptoms, future expectations and causes (if you will) of polycythemia vera. He explained the JAK2 mutation, the effectiveness of the JAK inhibitors and the process that caused my blood to be the way that it is. I had to do some internet sleuthing to help me understand. As my disease progressed, I was also introduced to Dr. Amelia A. Langston who informed me of what a bone marrow/stem cell transplant entailed. My siblings were all tested for a match. This whole idea instilled enough fear and bewilderment in me to seek the opinion of yet another: Dr. Candito Rivera at the Mayo Clinic in Jacksonville, Florida. By this time, I had gone from producing too much blood to not having enough. I also found that it was hereditary. My time with him was short-lived because the sole purpose of the (3) visits was to determine if in fact my disease was as life-threatening as I had been told and if the mutation was getting out of control.

Well, in 2012, Dr. Oleen abruptly retired and I was placed in the capable hands of a young, beautiful and very professional doctor at Phoebe by the name of Dr. Shawnta Speer. It was she who around December of 2013 discovered that my disorder had become myelofibrosis (chronic leukemia). My spleen had become enlarged, my white cell count was rising, red cell count going down and I was becoming more anemic.

Without a doubt, I knew it was time for me to decide what my next step would be. I came from a tight-knit family, and when my four incredible nephews in Houston, Texas heard of my last diagnosis, they insisted that I hurry and get to MD Anderson Cancer Center. That's what I did; I was on a mission to get the best possible care. **I was told that at MD Anderson I would find "the brightest/best doctors in the world."** I took their advice, especially after talking with another person who was and still is a patient at MD Anderson. She confirmed all that I had been told and read in reference to the hospital… that it was the #1 hospital in the country for cancer treatment, and that people go there from all over the world for help.

> My overall quality of life has improved–thanks to Dr. V and his team of competent, dedicated, service-oriented professionals.

Upon arriving at MD Anderson, I was introduced to the doctor with whom I had been assigned: Dr. Srdan Verstovsek. I always knew that there was a God, and that "if He brought me to it, he'd bring me through it." At my very first visit, I was told by him, among other things, **"I'm here to save lives."** That gave me all the encouragement I needed. After 2-3 more visits, I began placing my trust in him. I believe that through God, he will heal me. "Dr. V" explained that I had 2 choices…I could either have a bone marrow transplant, which is a very serious/life threatening (to say the least) procedure, or I could join a clinical trial to seek help. Time was of the essence! I learned long ago that the shortest road wasn't necessarily the best route. Though I could have the transplant and be cured of the disease, it involved too many processes that could end my life. Dr. V. suggested that I be

continued on page 2

Letter from the Director

The year 2014 has been a year of great progress in MPN research. An important new mutation has been discovered in MPN, the CALR mutation, which along with the $JAK2^{V617F}$ and MPL^{W515L} mutations drive the disease process in ET and MF. These 3 so called "driver mutations" are exclusive of each other and all result in hyperactive JAK-STAT intracellular signaling, the underlying problem in MPN that results in uncontrolled cell growth and associated inflammation. Identification of the CALR mutation will help in the diagnostic process, particularly in ET. In the clinical arena, we reported excellent results from a large phase 3 trial of ruxolitinib vs. best available therapy in patients with polycythemia vera (PV; the RESPONSE trial) resistant or refractory to hydroxyurea (standard first line therapy), showing that ruxolitinib was safe and could reduce splenomegaly, symptoms, blood counts, and eliminate the need for phlebotomy in a majority of patients in the study. Two new JAK2 inhibitors (momelotinib and pacritinib) that have shown promise in treating MF are currently being tested in patients with anemia or low platelets in Phase 3 trials. The results of these trials could lead to approval by the FDA for their use in MF. Momelotinib and pacritinib may be particularly useful in patients with severe anemia or very low platelets. In addition, we are building on the success of ruxolitinib by combining it with other new drugs, with the hope that the combination may be better than either drug alone. In the next couple of months we will begin accepting patients for a trial of pracinostat plus ruxolitinib. Pracinostat is a histone deacetylase inhibitor that may impact gene regulation that is abnormal in MPN. The combination may be more effective than ruxolitinib alone.

We also reported promising early results from a study of PRM-151 in patients with myelofibrosis (MF). PRM-151 is a new drug that works by a completely different mechanism than the JAK inhibitors and has the potential to reduce BM fibrosis. Early results showed that PRM-151 could reduce BM fibrosis in some patients. We are encouraged by these early results and plan to reopen the trial in winter 2015 to test the drug in more patients. We have opened several other new clinical trials and are set to open several more in the next few months. Providing more therapeutic options to our patients is a very important goal of our Clinical Research Center.

Dr. Srdan Verstovsek, Professor of Medicine in the Department of Leukemia at MD Anderson Cancer Center serves as Director of the Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia. Dr. Verstovsek is an internationally recognized physician scientist dedicated to understanding the biology of and developing new therapies for MPNs.

Trials, Tribulations, and Blessings • • • continued from page 1

the one to decide, and I did. I chose the road less traveled (clinical trials), and it has made all the difference. Since beginning the clinical trial in February of this year, my white blood count has gone down to normal on a couple of occasions, my spleen has decreased in size, I have gained back the weight that I had lost, and my overall quality of life has improved–**thanks to Dr. V and his team of competent, dedicated, service-oriented professionals.** He didn't say, but I believe that if the improvements continue, it's possible that my life will improve in every way.

Dr. V. is very witty, charismatic, and knowledgeable in clinical trials, sports a beautiful smile, a sense of humor and IS the "life-saver" he said he was. I believe in him and trust that what he says will happen, will indeed happen. I feel good about my decision to come to MD Anderson. I've learned to "let go and let God." And…Oh my God, MD Anderson is "a must see;" it's unbelievable! At each visit to MD Anderson I get to meet and share fellowship with different patients. Our hearts are all in the same place. I found success here, medically, and through comradery and fellowship. I now have a story to tell!

Proverbs 3:5-6 states that I should "Trust in the Lord with all thine heart, and lean not unto thine own understanding. In all thy ways acknowledge Him, and He shall direct thy path." He won't leave me or forsake me–I believe that. And like the biblical Moses, **my faith and trust in God, Dr. V., and his staff will be sufficient.**

I am both thankful and blessed to have a very supportive, loving and caring husband and family…especially a sister and husband (Cherrine and John) who have made every trip with me since I began coming to Houston (every 28 days). My nephews (Stanley, Tim, Edgar and Karl) have provided food and shelter time and time again. Not only have these people–my two children, brothers and sisters, and friends–assisted in those matters, but they have also made financial contributions to aid with travels, etc. **It's very important to establish unbreakable bonds with such a support group that will remain with you no matter what. I was told that when prayers go up, blessings come down.** I am also blessed to have the support and prayers of my pastor, church members, classmates, sorority, and so many special friends. I feel privileged to be (and have been) served by doctors at very fine and well-established centers. I found most of all, however, that if I follow these simple steps, I will be better prepared to cope with myelofibrosis, and my life as I knew it will be restored. Then and only then, will I be able to live a long, fruitful and productive life:

- Follow my doctor's orders
- Maintain a nutritious diet
- Exercise
- Get lots of sleep
- Stay hydrated
- Take medications as prescribed
- Pray to and thank God each day for sending me to MD Anderson and to Dr. V

I have read lots of literature, attended workshops, and talked to mentors/survivors. I encourage those in similar situations to follow suit, as I will mentor to others. If I were to provide a testimony of sorts, this would be it!

Support for Patients in Texas

The **South Texas** support group has held two meetings in the past 6 months: one was held in Humble, TX just north of Houston in June and the other was held in Austin in August. The meetings are generally held over lunch in a private room at a local restaurant. The meetings usually begin with updates on everyone's MPN status, followed by discussions on insurance issues, problems encountered coordinating doctors when multiple specialists are needed, specialty clinics, and personal experience with various treatments, including those being tested in clinical trials. According to Charlie, "we all leave these meetings with new knowledge about living with MPNs, but also with some wonderful new friends."

MPN Support Group Meeting, June 2014, Humble, TX
Nathalie Nielsen, Charlie Nielsen, Steve Wright, Jan Wright, Tina Cooper, Madelaine Hanna, Antoine Hanna, Rhonda Williams, Jo Latimer, Ken Latimer

Upcoming Event:

FILL MY CUP, Ladies Luncheon • Saturday, January 24, 2015
For Patients with PMF, ET or PV and their Caregivers
Houston, TX (exact location TBD)

This is a great opportunity to meet other with a similar diagnosis. Discussion will include the following topics:
• women's issues • communication with spouse
• discussion of questions to take to a patient conference in February

For questions or if you'd like to help organize this event, contact Tina Cooper at tina_cooper@windstream.net

The **North Texas** support group meets quarterly. Their next meeting will take place at the end of November or first of December. Individuals interested in information about upcoming meetings should contact Karen Stern.

Dallas Ft. Worth MPN Support Group – Larry Kramer, Cheryl and Roger Boyd, Jerry and Barbara Boyle, Wendy Sue, Dann and Nancy Carr, Charles and Mona Wyatt , Karen and Mike Stern and Patricia and Dwight Yarborough

To find out more information or join either of these groups,
please contact either Charlie or Karen by e-mail or through their Facebook page:
North Texas, Dallas/Ft. Worth – Karen-Stern@sbcglobal.net
South Texas, Houston – CharlieNielsen@aol.com
Facebook: https://www.facebook.com/groups/MPNSupportTX/

MPN Research: You Can Make a Difference

Gifts provide critical support needed to conduct innovative MPN research. Our MPN clinical and laboratory research team is dedicated to improving treatment outcomes for patients with MPNs.

To make a donation by mail, please send gifts to The University of Texas MD Anderson Cancer Center and specify "MPN Clinical Research Center" in the memo line using the attached envelope.

MPN Clinical Trials

Listed below are clinical trials enrolling patients with MPNs.

For more information on these clinical trials, call the information line toll-free at 1-800-392-1611.

Phase 3 Randomized Study of Oral Pacritinib vs. Best Available Therapy in Patients with Thrombocytopenia and Myelofibrosis

2013-1001 (clinicaltrials.gov NCT No: NCT02055781)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to compare the effectiveness of 2 different dose schedules of pacritinib to standard treatments in patients with myelofibrosis (MF). Pacritinib is an oral drug that inhibits the activity of JAK2 similar to ruxolitinib, but does not worsen thrombocytopenia, suggesting it may be a better alternative for treating patients with low platelet counts. Study visits will be every week for the first month and then once per month up to week 24. After 24 weeks, patients receiving best available therapy will receive pacritinib. P This study is accepting patients with advanced MF and platelet counts ≤ 100,000.

Phase 2 Study of Ruxolitinib and Pracinostat in Patients with Myelofibrosis

2014-0445

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to determine the effectiveness of the combination of ruxolitinib and pracinostat in patients with MF. The safety of this drug combination will also be studied. Pracinostat is a drug designed to cause chemical changes in proteins that are attached to DNA (the genetic material of cells), which may slow the growth of cancer cells or cause the cancer cells to die. Patients will receive ruxolitinib orally as a single agent for the first 3 months, after which point oral pracinostat will be added. This study will be open soon to patients with MF who have not been previously treated with a JAK inhibitor.

Phase 3 Randomized, Double-Blind Study of Momelotinib vs Best Available Therapy in Patients with Anemia or Thrombocytopenia and Myelofibrosis Who Have Been Previously Treated with Ruxolitinib

2014-0258 (clinicaltrials.gov NCT No: NCT02101268)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to compare the effectiveness of momelotinib to standard treatments in patients with myelofibrosis. Momelotinib is an oral drug that blocks the activity of JAK2 like ruxolitinib, which may help control the signs and symptoms of MF. Patients will be randomized to receive either momelotinib orally once daily or best available therapy. Study visits will be every 2 weeks for at least 24 weeks. After 24 weeks, patients receiving best available therapy will receive momelotinib. This study will be open soon to patients with MF who have anemia or thrombocytopenia.

Phase 2 Prospective, Open-Label Study of Sotatercept (ACE-011) in Patients with Myelofibrosis and Significant Anemia

2012-0534 (clinicaltrials.gov NCT No: NCT01712308)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to learn if sotatercept can help to control MF and anemia. The safety of this drug will also be studied. Sotatercept (ACE-011) is a treatment that uses your immune system to fight disease. Sotatercept may increase the growth and development of red blood cells. Patients will be given subcutaneous injections once every 3 weeks for at least 6 months. Study visits will be once per week for at least 4 months. This study is accepting patients with primary or secondary MF and significant anemia.

Phase 2 Open-Label, Dose-Escalation Study of NS-018, a JAK2 Inhibitor, in Patients with Myelofibrosis Previously Treated with Ruxolitinib

2011-0090 (clinicaltrials.gov NCT No: NCT01423851)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this clinical research study is to find the highest tolerable dose of NS-018 that can be given to patients with MF. The safety and efficacy of this drug will also be studied. NS-018 is a drug that blocks the JAK2 protein, similar to ruxolitinib. Patients will receive NS-018 orally once daily. Study visits will weekly the first month, monthly for months 2-4, and then every 3 months thereafter. Only patients previously treated with a JAK2 inhibitor are eligible to enroll. Patients must also have reasonable kidney and liver function, and a platelet count greater than 50,000. This study will reopen in the winter.

Phase 2 Study of PRM-151 (anti-fibrotic agent) in Patient with Myelofibrosis

2013-0051 (clinicaltrials.gov NCT No: NCT01981850)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to learn if PRM-151 can help to control MF. Two different dosing schedules will be compared. The safety of this drug will also be studied. PRM-151 is designed to help control tissue scarring (such as bone marrow fibrosis). Some participants will also receive ruxolitinib. Ruxolitinib is an oral drug that blocks the activity of JAK2 and may control the signs and symptoms of MF. PRM-151 will be given intravenously for at least 6 months. Study visits will be weekly. This study will begin enrolling patients in the spring.

To Schedule an Appointment Call 1-85-LEUKEMIA (toll-free) or 713-563-2000

Phase 2 Study of Eltrombopag (thrombopoietin mimetic) in Patients with Symptomatic MF That Are on Low-Dose Ruxolitinib Due to Low Platelet Count

2011-0319 (clinicaltrials.gov NCT No: NCT01428635)

Principal Investigator: Gautam Borthakur

Study Description: The goal of this study is learn if eltrombopag can help control or prevent low platelet counts in patients receiving ruxolitinib for MF. Eltrombopag is a protein that binds a molecule on blood cells that controls the production of platelets. Patients will continue taking ruxolitinib as prescribed, but will also take eltrombopag as a pill once per day. This study is currently accepting patients with MF and low platelet counts.

Phase 2 Study of Ruxolitinib and 5-Azacytidine (hypomethylating agent) in Patients with Myelodysplastic Syndrome/Myeloproliferative Neoplasm

2012-0737 (clinicaltrials.gov NCT No: NCT01787487)

Principal Investigator: Naval Daver

Study Description: The goal of this study is to learn if the combination of ruxolitinib and azacytidine can help to control disease in patients with myelodysplastic syndrome (MDS)/MPN. Azacytidine is a drug that has been used to treat MDS. Combination of ruxolitinib and azacytidine may improve the overall effectiveness of each drug. Ruxolitinib will be taken orally twice per day for the first 3 months, after which time low-dose azacytidine will be added. Azacytidine will be given intravenously daily for the first 5 days of each 28-day cycle. This trial is accepting patients with MDS/MPN.

Phase 2, Open-Label, Randomized Study to Evaluate the Safety and Efficacy of Momelotinib in Patients with Polycythemia Vera or Essential Thrombocythemia

2013-0977 (clinicaltrials.gov NCT No: NCT01998828)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to determine the safety and efficacy of momelotinib in subjects with PV or ET. Momelotinib is a drug that is designed to block JAK2 similar to ruxolitinib. Patients will receive either 100 or 200 mg of momelotinib orally twice daily. Study visits will be every 2 weeks during the first 8 weeks and then monthly up to week 24. This study is accepting patients with PV or ET who require treatment and have not yet received treatment with a JAK inhibitor.

Phase 2 Open-Label Study of Anagrelide Controlled Release (CR) in Subjects with Thrombocytosis Secondary to Essential Thrombocythemia and Other Myeloproliferative Neoplasms.

2014-0354 (clinicaltrials.gov NCT No: NCT02125318)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to learn if controlled-release anagrelide (anagrelide CR) can help control high platelet counts in patients with bone marrow disorders. The safety of this drug will also be studied. Anagrelide is a drug that has been shown to slow down how fast platelets are made in the blood. Anagrelide CR is made to dissolve more slowly, which may allow the use of lower dosages and fewer side effects. Patients will receive oral anagrelide CR twice daily for at least 24 weeks. Study visits will be weekly for the first 3 months and then every 2 weeks thereafter. This study is open and enrolling patients with ET, PV, CML, or MF and platelet counts ≥ 600,000.

Phase 2 Study of Brentuximab Vedotin (SGN-35) in Patients with CD30-Positive Aggressive Systemic Mastocytosis with or without an Associated Hematological Clonal Non-Mast Cell Lineage Disease

2012-0734 (clinicaltrials.gov NCT No: NCT01807598)

Principal Investigator: Srdan Verstovsek

Study Description: The purpose of this study is to determine if the drug brentuximab vedotin (Adcetris) can help control systemic mastocytosis. Brentuximab vedotin is a biological therapeutic designed to bind to a certain protein (CD30) on cancer cells and kill them. Patients will receive brentuximab vedotin intravenously once every 21 days for up to 8 cycles. Study visits will be weekly during the first month and then twice a month thereafter. This study is currently accepting patients with advanced systemic mastocytosis with or without an associated hematological clonal non-mast cell lineage disease.

Phase 3 Randomized Double-Blind, Placebo-Controlled Study of Masitinib in Patients with Indolent Systemic Mastocytosis with Handicap

2008-0275 (clinicaltrials.gov NCT No: NCT00814073)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to compare the benefits of treatment with masitinib to no treatment in patients with mastocytosis with handicap. Masitinib is a drug that inhibits a protein called KIT that is often mutated in patients with mastocytosis. Masitinib may be effective in reducing the number of mast cells in patients with mastocytosis. Patients will take masitinib orally twice per day for at least 24 weeks. Study visits will be every 4 weeks. This study is currently accepting patients with mastocytosis who have defined handicaps.

What's New in Essential Thrombocythemia

By Srdan Verstovsek, MD, PhD and Kate Newberry, PhD

Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized primarily by an increased number of platelets in the blood (Figure 1).

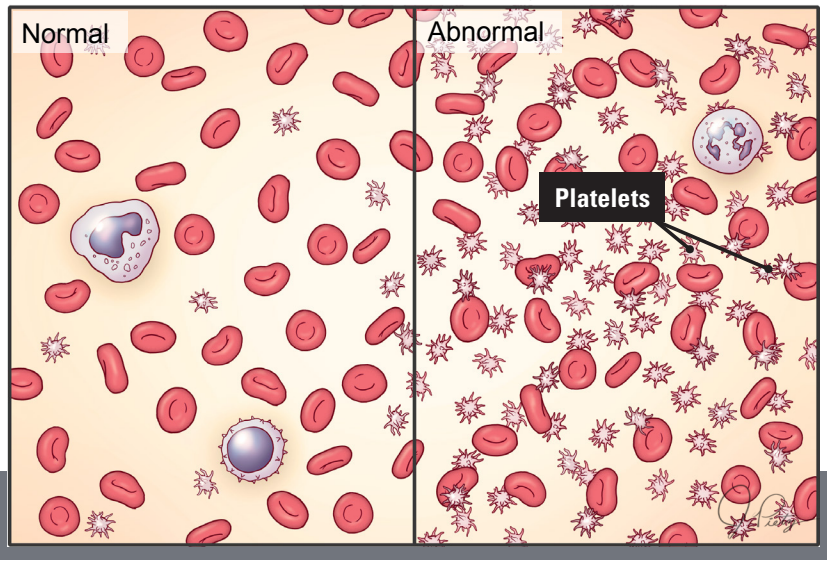

Figure 1. Illustration of the excess platelets found in patients with ET.

Some patients may have slightly elevated white blood cell numbers or a slightly enlarged spleen. Some of the most common symptoms patients experience include fatigue, headache, vision disturbances, dizziness, itching or burning, redness and pain in the hands and feet. ET is associated with increased risk of thrombosis and bleeding. Indeed, the most common and serious complication of ET is thrombosis (formation of a clot in the blood vessels). Some patients may be diagnosed with ET only after experiencing a blood clot, for example, in the leg (deep venous thrombosis causing swelling and pain in the calf) or lungs (pulmonary embolism causing sudden severe shortness of breath). However, many patients have no symptoms and only learn of their diagnosis after routine blood testing that reveals that their platelet counts are abnormally high. The main goal of treatment is to reduce the risk of thrombosis. Below we discuss new research into the cause of ET as well as what's new regarding diagnosis and treatment.

Diagnosis

While a major feature of ET is high platelet levels in the blood (thrombocytosis), elevated platelets can also indicate several other conditions, such as iron deficiency, chronic inflammation or infection, other cancers or previous splenectomy. Therefore, your doctor should first rule out these other causes of thrombocytosis. A bone marrow biopsy must also be performed to rule out other MPNs (polycythemia vera or myelofibrosis) or myelodysplastic syndrome. Recent studies suggest that the early stages of myelofibrosis may present with characteristics of ET, and therefore it may be particularly important to distinguish between early (prefibrotic) myelofibrosis and ET.

Prognosis

The good news is that the majority of patients have an excellent prognosis and even for those who are considered at high-risk of thrombosis, treatment with medications that reduce blood count (hydroxyurea, interferon or anagrelide) can significantly reduce this risk. Determination of thrombosis risk in patients with ET is based on age and history of thrombosis: being older than 60 or having had a previous thrombotic event are both considered high-risk factors. In the past 2 years researchers have identified other factors that may increase the risk of thrombosis in patients with ET. A new prognostic scoring system has been proposed, called the International Prognostic Score of thrombosis in ET (IPSET-thrombosis) that lists 4 factors associated with an increased risk of thrombosis. These factors are age older than 60 (1 point), history of thrombosis (2 points), cardiovascular risk factors, such as diabetes, hypertension and smoking (1 point), and the JAK2V617F mutation (2 points). Patients scoring less than 2 points are defined as at low risk; those with 2 points as at intermediate risk, and those with more than 2 points as at high-risk of developing thrombosis. It is important to note that the overall risk of thrombosis is still relatively low even for patients in the highest-risk groups. In a large study of patients with ET, fewer than 1% of patients who were classified as low risk had thrombosis in a 1-year period, while 2.9% of patients classified as high risk had thrombosis in a 1-year period. For many patients (those defined as low or intermediate risk), no treatment is necessary or for patients with symptoms related to temporary small vessel occlusion (e.g. headache, dizziness), low-dose aspirin (100 mg/day) is usually sufficient. Most doctors agree that only patients who have a high risk of thrombosis should be treated. The main purpose of this new scoring system is to allow doctors to better identify which patients should be treated; however, this is just a proposal and not yet in everyday use.

Treatment Options for ET

The most common treatment for patients at high-risk of thrombosis is hydroxyurea, which has been shown to reduce the risk of thrombosis in patients with ET. However, approximately 20%-25% of patients do not have a good response to hydroxyurea or have intolerable side effects. Therefore, other treatments are needed for these patients. One good option is anagrelide, which has been used successfully to treat ET, and a recent large study suggested that it may be equivalent to hydroxyurea in terms of its ability to reduce the risk of thrombosis. Another option for patients who do not respond well to either hydroxyurea or anagrelide is pegylated interferon alpha. The effectiveness of interferon alpha for reducing platelet counts in patients with ET has been recognized for more than 25 years, but side effects such as flu-like symptoms and depression make it a poor choice for some patients. However, a newer formulation—pegylated interferon alpha–has been shown to be better tolerated, with fewer side effects.
In clinical studies, up to 80% of patients treated with pegylated interferon alpha have seen a reduction in platelet and white blood cell count and improvement in disease-related symptoms. The drug has also been shown to reduce the number of cells containing the JAK2 mutation, suggesting that it may have some benefit for reducing the amount of diseased cells in the blood. In fact, some physicians have stated that pegylated interferon alpha given at lower doses is their first choice of treatment for their patients with ET.
A randomized study comparing the effectiveness of pegylated interferon alpha with hydroxyurea in patients with ET is currently underway, and the results should provide better evidence for which treatment should be tried first.

Mutations in ET

While the cause of ET is not known, it is thought that the disease is caused in part by changes in the development and function of cells in the bone marrow that generate platelets (megakaryocytes) and other cells. In the past decade, scientists have discovered mutations in three genes that are thought to contribute to the development of ET. The first mutation identified was the Janus-kinase 2 mutation (JAK2V617F), which is found in up to 60% of patients with ET. JAK2 is a molecule inside the cells that helps to transmit signals from outside the cell to inside the cell, telling the cellular machinery to turn genes on or off. The JAK2V617F mutation causes the JAK2 molecule to be stuck in the "on" state, which leads to uncontrolled cell growth and the overproduction of molecules involved in inflammation. Interestingly, scientists have recently found that JAK signaling is overactive in all patients with MPNs, regardless of whether they have the JAK mutation. This finding explains why JAK inhibitors such as ruxolitinib (Jakafi) have been found to be effective in reducing symptoms of patients with myelofibrosis, regardless of whether the patient has a JAK mutation.

Several years after discovering the JAK2V617F mutation, scientists discovered that 3-5% of patients with ET have a mutation in the gene that encodes the thrombopoietin receptor (called the MPL gene). The main job of the thrombopoietin receptor is to control the production of platelets in the blood, and mutations in MPL have also been shown to disrupt JAK signaling. This is because the thrombopoietin receptor, a molecule that protrudes from the surface of the cell, binds to JAK2 inside the cell. When the growth factor thrombopoietin (TPO), which is found in blood, binds to the thrombopoietin receptor on the outside of the cells, JAK2 is activated. Together the JAK2V617F and MPL mutations explain the overactive JAK signaling in up to 65% of patients with ET. But what about the other 35% of patients? A major development in the past year was the discovery of mutations in the calreticulin gene (CALR) in 25% of patients with ET (nearly 70% of those who do not have a JAK2 or MPL mutation). CALR is a protein that has been found to have several functions inside the cell and it is unclear what the function the mutations disrupt. Though, most of the mutations found are predicted to alter the three-dimensional structure of the protein and almost certainly its function. Although scientists don't know how, CALR mutations also lead to overactive JAK signaling.

Therefore, scientists have now discovered mutations that can account for overactive JAK signaling in up to 90% of patients with ET (Figure 2). And more recent studies correlating these mutations with clinical manifestations of ET suggest that there may be distinct subtypes of ET. For example, patients with the CALR mutation are more often male, tend to be younger, have higher platelet counts, and a lower risk of thrombosis. Patients with the JAK2V617F mutation tend to have higher hemoglobin levels, lower platelet counts and increased risk of thrombosis, while patients with MPL mutations tend to have lower hemoglobin, higher platelet counts and a higher frequency of microvascular problems. While these initial findings are interesting and suggest that we may be able to better diagnose and treat patients according to which mutation they have, many more studies need to be done to confirm these initial findings and determine their impact on the treatment of ET.

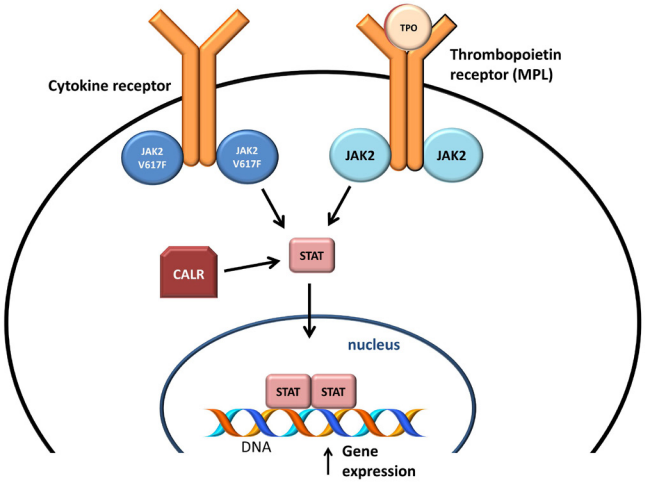

Figure 2. Schematic of a cell showing how mutations in JAK2, MPL, and CALR all lead to overactive signaling of the JAK-STAT pathway.

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The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia Newsletter

A periodic newsletter published by The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia at MD Anderson Cancer Center to provide members of the MPN community with information on current research and treatments.

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Future Nationwide Education Initiatives

Joyce Niblack Memorial Conference on Myeloproliferative Neoplasms

February 21–22, 2015

The MPN Education Foundation and Mayo Clinic sponsor this patient-doctor conference at the Mayo Clinic in Scottsdale AZ every 2 years. The conference brings together medical experts in MPNs from around the country with MPN patients and their caregivers/families. The conference is a great opportunity to learn more about the many issues that are faced by those diagnosed with one of these disorders. Topics covered include genetics of MPNs, interpreting blood counts, which questions to address with your doctor, coping emotionally with a chronic disease, and other issues that can arise because of such a diagnosis.

Unfortunately, this year's conference is already full. However, after the conference you can order a recording of the 2-day conference on the MPN Education Foundation website.

For more information visit http://www.mpninfo.org/2015conference.php

MPN EDUCATION FOUNDATION

MPN-NET

Formed in 2004, the MPN Education Foundation aims to bring information, reassurance and support to MPN patients and their loved ones all over the world.

2015 EosConnection Patient Conference

hosted by the American Partnership for Eosinophilic Disorders (APFED)

June 26–27, 2015
Indianapolis, Indiana

APFED's EosConnection Patient Conference is an annual event that provides an opportunity for patients, caregivers, and health care providers to gather to learn about eosinophilic disorders, the latest in scientific research of the disease, and to learn practical strategies for daily management of disease symptoms. Social opportunities are being planned for June 25 and June 28.

More details will be posted to www.apfed.org when available.

Apfed
American Partnership for Eosinophilic Disorders

APFED is a non-profit patient advocacy organization established to assist and support patients and their families coping with eosinophil associated diseases (EADs), including eosinophil-associated gastrointestinal disorders, hypereosinophilic syndrome, and Churg-Strauss Syndrome.

2015 Patient Education Symposia

hosted by MPN Advocacy & Education International

- March 19, 2015 in Washington, DC
- April 23, 2015 in Honolulu, Hawaii
- September 2015 in San Diego, California – Women in MPN (date TBD)
- October 29, 2015 in Seattle, Washington

For more information visit www.mpnadvocacy.com or contact Ann Brazeau at 517-889-6889 or abrazeau@mpnadvocacy.com

Founded by Ann Brazeau, former vice president of development at MPN Research Foundation, MPN Advocacy & Education International (MPN AEI) provides educational programs, materials, and resources for patients, caregivers, physicians, and entire healthcare teams to improve their understanding of MF, PV, and ET.

MPN ADVOCACY & EDUCATION INTERNATIONAL

Other online resources:

MPNforum Monthly… the MPN community's hometown paper

MPNforum Monthly is a not for profit online magazine founded by MPN patient Zhenya Senyak. MPNforum monthly **(mpnforum.com)** publishes stories, features and columns that impact the lives of patients suffering from an MPN.

The Mastocytosis Society

The Mastocytosis Society, Inc. is a non-profit organization dedicated to supporting patients with mastocytosis and mast cell activation disorders, as well as their families, caregivers and physicians through research, education and advocacy. **www.tmsforacure.org**