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

MPN Focus

Mast Cell Mania: At the Root of MPN-Related Itching?
Part 1, A Patient’s Perspective

By David Wallace

Background

A high percentage of patients with myeloproliferative neoplasms, especially those with polycythemia vera, suffer from aquagenic pruritus, a fancy clinical term for itching. Few patients presenting with itching are tested for PV, but it is a classic symptom that tags along with a host of other strange bedfellows including fatigue, headache, dizziness, shortness of breath, red skin tone, gastrointestinal issues, body pain, cognitive impairment, and the list goes on. There are few treatments for itching that are highly effective and provide consistent relief.

Itching may be caused or worsened by exposure to water without observable skin lesions. The symptoms may be felt immediately after contact with water and may last an hour or longer. It generally occurs in the trunk and nearby extremities. Most patients describe itching, but others report a tingling, burning or stinging sensation.

The ravages of extreme itching can be so intense that a “fear of bathing” develops, creating a negative impact on quality of life and perhaps less social engagement.

I have been involved in patients’ discussions on this issue and it is very real. This article will focus on itching and treatment, the driving mechanisms behind itching with discussion of other symptoms as well. It is written from the patient perspective with medical commentary to follow.

A Personal Perspective

I was out of town for a medical procedure and packed my bags (and meds) methodically or so I thought. It was not until shower time that I discovered I had forgotten my Atarax, also known as hydroxyzine, a drug I did not like to take because of the undesirable side effects, actually it just knocks you out (it is also prescribed for anxiety and panic attacks….go figure) after an episode has begun, so you don't feel the itching as much. This was going to be a miserable trip, like the BMB (bone marrow biopsy) wasn't enough….if I didn't come up with an alternative.

The Z and Z combo (Zyrtec and Zantac), a lifesaver!!

I was keeping a plan B tucked away to try in a “break the glass emergency.” It was so simple, it was hard to believe it might actually work. During one of our online discussions about furious bouts of itching (2 or 3 weeks prior to the trip), one of my friends, Roy Randall, reported great success using over the counter Zyrtec and Zantac. Other patients chimed in, sharing successful results from the combo. I made

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**Letter from the Director**

A although they are less common, atypical myeloproliferative disorders, such as mastocytosis, hypereosinophilic syndromes, and chronic neutrophilic leukemia (CNL) are also part of our focus here in the MPN Center. Drugs that target specific molecular abnormalities in these atypical MPNs are becoming available. For example, imatinib, a drug typically used to treat chronic myelogenous leukemia (CML), can be used in some types of eosinophilia, and we have opened a clinical testing ruxolitinib in CNL and atypical CML. In addition, we are testing a new drug, BLU-285, which targets a gene mutation found in patients with advanced systemic mastocytosis. In the last issue, we discussed mastocytosis, a disease in which too many mast cells are produced. In this issue, we focus on mast cells and their contributions to MPN-related itching.

I’d also like to remind everyone that we will be hosting the fourth annual MPN patient meeting on October 1, 2016. Dr. Prithviraj Bose from MD Anderson and Dr. Olatoyosi Odenike from the University of Chicago Medical Center will be joining me on this year’s panel. We hope that you can join us at this meeting online. I’m looking forward to another great event!

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**Mast Cell Mania: Part 1**

[continued from page 1]

That afternoon, I high tailed it to Walgreens, bound and determined to try this mysterious combo, practically unknown to the MPN world. I was already taking (1) 10 mg Zyrtec in the morning for allergies and added (2) 150mg Zantac to my routine, one in the morning and one at night. It provided itching relief quickly. …during the next several days my itching faded away, nearly 100%, I was saved from a pruritus meltdown!! Miraculous relief that I hope will be helpful to many fellow MPN patients. It should be noted that generic versions Cetirizine Hydrochloride (Zyrtec) and Ranitidine (Zantac) can be purchased from Costco or Walmart for a considerable discount from the branded versions.

When I was having regular phlebotomies (before Pegasys/Jakafi treatment), I noticed once my HCT rose to 42 or more, I become highly symptomatic and the itching creeps back into the symptom equation (although to a lesser extent) regardless of the Z and Z combo.

The Z and Z combo’s effectiveness in mast cell disorders is discussed in an online article by William Alford:

“Patients with urticaria (hives) and mast cell disease are typically treated with various combinations of antihistamines which block histamine receptor sites on cells, with a fine-tuning of both dosage levels and drug choice often being very specific to the patient. A very successful choice is the well-known “ZZ” combo of Zyrtec and Zantac since this combination blocks both the H1 and H1 receptors. Other antihistamines include ChlorTrimeton, Benadryl, Dramamine, Claritin, and Tavist.”

**Note:** Before taking any medications, even OTC, be sure to check with your doctor or pharmacist.

**Mast Cell Disease and the Release of Histamines**

Mast cells have long been known to contribute to the discomforts of mankind by releasing histamine and producing the miseries of allergies. However, patients with mast cell disease may also present with a multitude of disparate symptoms such as arthritis, gastroesophageal reflux disease (GERD), constipation, malabsorption, cramping, severe abdominal bloating, short term memory problems, headache, nausea, bone pain, heart palpitations, changes in cognitive function and mood and more. Sound familiar? Nearly identical to the symptoms we experience as MPN patients.

Mastocytosis, one of the myriad of mast cell diseases are classified as an MPN, so no surprise there!

**Mast cell diseases are histamine disorders** (be sure to click on the preceding link and scroll down midway for the excellent graphic, Histamine Intolerance & Mast Cell Activation) that come in many flavors – mast cell activation syndrome (MCAS), mast cell activation disorder (MCAD) and mastocytosis (numerous types) among others. Other conditions with a link to histamine/mast cell include: Fibromyalgia, Cancer, Multiple Sclerosis, Narcolepsy, IBS, Crohn’s, Parkinson’s, Alzheimer’s and heart disease.

Mast cell activation syndrome is a fancy way of saying the immune system is freaking out and dumping inflammation into the body, sometimes chronically. While mast cells present throughout the body, all body tissues that come in direct contact with the outside world have mast cells and they are concentrated in the skin, gut, nasal passages, lung, urinary tract and other mucus membranes.

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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.
With MPNs, we suffer with excess histamine due to basophil breakdown (a type of white blood cell). Histamine is one of the inflammatory players released by mast cells, along with heparin and serotonin. They also contain cytokines, interleukin, leukotrienes, prostaglandins and other inflammatory agents. The release of these proinflammatory agents results in the classic allergy symptoms which most of us are familiar with.

However, the principle chemical mediator of mast cells is histamine which can cause tissue swelling, itching, flushing and other noxious skin responses. It is what causes the itching and swelling of the mosquito bite and the itch of healing wounds with the rapid growth of new tissue. But it can also cause systemic responses such as headache, nausea, dizziness, and diarrhea and can be involved in other GI disease such as gastric ulcer and IBS.

The light has been shed on one of the key culprits in the complex universe of MPN symptoms. The graphic above provides a visual representation summarizing histamine-mediated symptoms. The discussion on itching just scratches the surface, no pun intended!

Summary of Histamine-Mediated Symptoms


Join us for the 4th Annual MPN Patient Forum

Understanding Myeloproliferative Neoplasms: Empowering Yourself and Your Loved Ones to Get the Best Care

This FREE interactive event will feature MPN experts, clinicians and patient advocates to discuss the latest discoveries in MPN research and how you can be empowered to get the best care for you or a loved one. This meeting is a great opportunity to meet and connect with other patients and caregivers living with MPNs. For more details on the event please visit the Patient Power website (www.patientpower.info/event/mpn-houston-2016)

When:  Saturday, October 1, 2016
Where:  MD Anderson Cancer Center, Duncan Building
1155 Pressler Street, Houston, TX 77030
or Online
Listed below are all open clinical trials enrolling patients with MPNs at MD Anderson Cancer Center as of August 31, 2016. For more information on these clinical trials, call the information line toll-free at 1-800-392-1611 or contact Dr. Verstovsek at sverstov@mdanderson.org. For information on other clinical trials in MPN go to www.clinicaltrials.gov.

**A Phase Ib/II, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vismodegib in Combination with Ruxolitinib versus Placebo and Ruxolitinib in Patients with Myelofibrosis**
2015-0974 (NCT No: NCT02593760)

**Principal Investigator:** Srdan Verstovsek

**Study Description:** This clinical research study is made up of 2 phases: Phase 1b and Phase 3. The goal of Phase 1b is to learn if it is safe to add vismodegib to ruxolitinib for the treatment of myelofibrosis. The goal of Phase 3 is to compare the effects of this drug combination to those of ruxolitinib when it is given alone. Vismodegib is an inhibitor of the hedgehog signaling pathway, which is overactive in myelofibrosis. In Phase 1b, patients with receive visomodegib orally once per day and ruxolitinib twice per day. In Phase 3, patients will be randomized 1:1 to receive either vismodegib plus ruxolitinib or placebo plus ruxolitinib. Study visits will be every 2 weeks for the first 3 months and then monthly thereafter. This study is currently enrolling patients.

**Phase 2 Translational Biology Study of Momelotinib in Patients with Myelofibrosis and Transfusion-Dependent Anemia**
2015-0557 (NCT No. 02515630)

**Principal Investigator:** Srdan Verstovsek

**Study Description:** The goal of this study is to determine the efficacy of momelotinib in improving transfusion-dependent anemia in patients with myelofibrosis. This study will also assess changes in certain biomarker levels while on treatment. Momelotinib is an oral JAK inhibitor that may improve the signs and symptoms of myelofibrosis in patients with anemia. Patients who have received transfusions of 4 or more units of red blood cells in the past 8 weeks are eligible to enroll. Patients will receive momelotinib for at least 6 months. Study visits will be every 2 weeks for the first month and then monthly thereafter. This study is open for enrollment.

**Phase 2 Study of Nivolumab in Patients with Myelofibrosis**
2014-0962 (NCT No: NCT02421354)

**Principal Investigator:** Srdan Verstovsek

**Study Description:** The goal of this study is to determine the effectiveness of nivolumab in patients with myelofibrosis. The safety of this drug will also be tested. Nivolumab is a treatment that uses your immune system to treat disease. Patients will receive nivolumab intravenously every 2 weeks for at least 8 doses and then every 3 months thereafter.

**Phase 2 Study of Ruxolitinib and Pracinostat in Patients with Myelofibrosis**
2014-0445 (clinicaltrials.gov NCT No: NCT02267278)

**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 histone deacetylase inhibitor. Patients will receive ruxolitinib orally as a single agent for the first 3 months, after which point oral pracinostat will be added. This study is accepting patients with MF who have not been previously treated with a JAK inhibitor. Study visits will be monthly for the first 6 months and then every 3 months thereafter.

**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) 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. This study is accepting patients with myelofibrosis and significant anemia.

Phase 2 Study of LCL-161 in Patients with Myelofibrosis
2013-0612 (clinicaltrials.gov NCT No: NCT02098161)

Principal Investigator: Naveen Pemmaraju

Study Description: The goal of this clinical research study is to learn if LCL-161 can help to control myelofibrosis. The safety of this drug will also be studied. LCL-161 is an oral drug that activates a signaling pathway that promotes cancer cell death. Patients will receive LCL-161 orally every 7 days. Study visits will be monthly for the first 4 months and then every 3 months thereafter.

Phase 1 Study of BLU-285 in Patients with Advanced Systemic Mastocytosis or Relapsed or Refractory Myeloid Malignancies
2015-0832 (clinicaltrials.gov NCT No: NCT02561988)

Principal Investigator: Srdan Verstovsek

Study Description: The goal of this study is to determine the highest tolerable dose of BLU-285 that can be given to patients with advanced systemic mastocytosis or relapsed/refractory myeloid malignancies. The safety and efficacy of this drug will also be studied. BLU-285 is an oral drug that is designed to block the activity of the mutated form of the KIT receptor tyrosine kinase (KITD816V), which is present in patients with systemic mastocytosis. Patients will receive BLU-285 orally once daily. This study is currently enrolling patients with advanced systemic mastocytosis, mast cell leukemia or another myeloid malignancy that has relapsed or not treatable by standard treatments.

Phase 2 Study of Ruxolitinib and 5-Azacytidine (hypomethylating agent) in Patients with Myelodysplastic Syndrome/Myeloproliferative Neoplasm or Myelofibrosis
2012-0737 (clinicaltrials.gov NCT No: NCT01787487)

Principal Investigator: Naval Daver

Study Description: This 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 or myelofibrosis. The 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. Study visits will be monthly for the first seven months and then every 3 months thereafter.

Phase 1/2 Study of SL-401 in Patients with Advanced, High-Risk MPNs, Including Myelofibrosis, Chronic Myelomonocytic Leukema, and Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia
2014-0976 (clinicaltrials.gov NCT No: NCT02268253)

Principal Investigator: Naveen Pemmaraju

Study Description: The goal of this study is to study the safety and efficacy of SL401 in patients with advanced high-risk MPNs. SL401 is a biological agent that binds to cells that cause MPNs. Patients with symptomatic myelofibrosis who are not candidates for, are intolerant of or have failed therapy with ruxolitinib are eligible. Patients with chronic myelomonocytic leukemia (CMML) or primary eosinophilic disorders who are not candidates for therapy with imatinib are also eligible. SL401 will be given intravenously daily for the first 3 days of each 28-day cycle.

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 every 3 weeks for the first 8 cycles and then every 6 weeks thereafter.

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Call 1-85-LEUKEMIA (toll-free) or 713-563-2000
As David discussed in Part 1 of this series, itching, especially after bathing, is a common and troublesome symptom of polycythemia vera (PV) and other myeloproliferative neoplasms (MPNs). Itching has been reported in up to 85% of patients with MPN. While the biological basis of itching is not fully understood, the itch sensation is recognized in the brain by signals sent from specific nerve fibers (neurons) within the skin that respond to various types of stimuli. Histamine is one of many stimuli that activate sensory neurons. Histamine is generated in white blood cells that are part of the body’s immune system. The three types of white blood cell that produce histamine are called eosinophils, basophils and mast cells. All three cell types contain granules (storage sacs within the cell) that contain histamine and other molecules that act as “chemical alarms.” Mast cells reside in most tissues within the body, while eosinophils and basophils are found in the circulating blood. The majority of the body’s histamine is stored in the granules of mast cells. Histamine is released from these cells in a process called degranulation. Degranulation occurs when antigens interact with IgE molecules that are bound to receptors on the surface of mast cells, basophils and eosinophils (Figure 1). Once the cells are activated they release the contents of their granules, including histamine and other mediators of the immune response.

The Many Roles of Histamine

So how exactly does histamine cause itching? Histamine is a biologically active molecule that has an effect on a multitude of bodily processes ranging from the allergic response to gastrointestinal function, and the regulation of the sleep wake cycle (see Figure on page 3). Histamine exerts its action by binding to histamine receptors on the surface of cells.

There are four different histamine receptors (called H1-H4):

- **The H1 receptor** is found throughout the body, including the brain, skin and organs. The H1 receptor is found on sensory neurons and thus is involved in the perception of itch.

- **The H2 receptor** is found on specialized cells in the stomach and cells that comprise the blood vessel walls. Activation of the H2 receptor leads to dilation of the blood vessels and gastric acid secretion.

- **The H3 receptor** is found in the central and peripheral nervous system.

- **The H4 receptor** is found in the bone marrow and white blood cells, as well as in the thymus, small intestine, spleen and colon. It plays a role in the migration of mast cells, itch perception, cytokine production and gastrointestinal pain.

**Figure 1.** Schematic of a mast cell and the degranulation process.
The effects of histamine are dependent on how much of it is present in the blood. At amounts slightly higher than normal, you get increased heart rate and increased secretion of gastric acid. As the level further increases, you can have headaches, flushing, hives and itching, and at very high levels it can lead to anaphylactic shock.

As David and other MPN patients have discovered, a combination of 2 different types of antihistamine can greatly alleviate MPN-related itching. Zyrtec (cetirizine hydrochloride) blocks the H1 receptor, while Zantac (ranitidine HCl) blocks the H2 receptor. All of this suggests that if you can sufficiently reduce the histamine levels you can combat the itching. Below I will discuss some of the scientific evidence regarding the role of mast cells and histamine in MPN-related itching.

Evidence for the Role of Mast Cells/Histamine in MPN-Related Itching

The role of mast cells in MPN-related itching has not been well-studied. Some evidence shows that mast cells in MPNs are functionally abnormal. For example, one study (Ishii T et al. Blood 2009) showed that mast cells from MPN patients release significantly more histamine, leukotrienes, and IL-31 (all mediators of the allergic response) than normal mast cells. The authors showed a correlation between the presence of itching and a larger number of mast cells. Others have shown increased levels of histamine in the blood and urine of MPN patients. However, evidence of a correlation between histamine levels and itching in MPNs is conflicting. In fact, Ishii and colleagues did not find a correlation between the presence of itching and levels of histamine released from MPN mast cells. Interestingly though, they found that MPN mast cells released higher levels of prostaglandin D2 (an inhibitor of itching), but the levels were significantly decreased at higher temperatures, suggesting that perhaps the itching induced after a hot shower is due to the lower levels of prostaglandin D2. A follow-up study by the same authors (Ishii et al. Leukemia 2009) found that mast cells from patients with PV and PMF showed increased activation. However, it is important to remember that these studies were all performed on cells grown in vitro (in a petri dish) and therefore are not definitive.

In another study, skin biopsies were taken from the abdomen of PV patients after exposure to either warm water or room temperature water (Abdel-Naser et al. 2007). The skin biopsies were compared with those from normal individuals. No changes were seen in skin samples from normal individuals when exposed to warm or room temperature water; however, skin samples from PV patients exposed to warm water showed vasodilation and increased numbers of white blood cells. In addition, the mast cells in the room temperature water–exposed skin from PV patients were larger, irregularly shaped, and were densely packed with granules. The skin from PV patients exposed to warm water showed many mast cells that appeared to be ruptured with their granules spilling out. These changes were not seen in the normal skin samples.

All of these findings suggest that the mast cells in PV patients may function abnormally and that warm water may induce degranulation and the release of histamine, explaining the onset itching after showering.

Clearly more studies are warranted, but it appears that at least for some patients, the Z&Z combo may be the best defense against itching. For patients with more advanced disease who have been treated with hydroxyurea and have not had an adequate response, ruxolitinib is now approved by the FDA for this indication. Results from the phase 3 multicenter clinical trial in patients with PV showed a 95% reduction in PV-related itching after 32 weeks of treatment.

References:
Abdel-Naser MB, Zaki MS, Mousa MH, Hamed H, Rizk MS, Mohamed HE, Habib MA. Cutaneous mononuclear cells and eosinophils are significantly increased after warm water challenge in pruritic areas of polycythemia vera. 2007 J Cutan Pathol 34:924-929.
Upcoming Events

2016 Patient Education Symposia hosted by MPN Advocacy & Education International

September 30, 2016 in New York City
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 Education Foundation

10th Joyce Niblack Memorial conference at the Mayo Clinic in Scottsdale, Arizona in the Ashton Taylor Auditorium, 13400 E Shea Blvd., Scottsdale, AZ 85259
Saturday, Feb. 25 – Sunday, Feb. 27, 2017
For more information visit www.mpninfo.org/mpn-2017-conference. 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 via a website (www.mpninfo.org), by convening a patient conference every 2 years, and via the email-based support group MPN-NET.

Other Online Resources:

MPN Cancer Connection

www.mpncancerconnection.org

Support for Patients in Texas

Founded by MPN patient and advocate Charlie Nielsen, the South Texas support group meets several times a year to discuss issues associated with living with an MPN. The North Texas support group is now led by Andrea Spica and meets quarterly. Both groups provide an opportunity to meet and share with others with a similar diagnosis.

To find out more information or join either group, please contact them either by e-mail or through their Facebook page:

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