

Notes from the

**Seventh Biennial Joyce Niblack Memorial
Conference on the Myeloproliferative Neoplasms
February 9-10, 2013, Mayo Clinic, Phoenix,
Arizona.**

Taken by Nathalie C. Cook



The presenters pictured left to right: Richard Silver MD, Animesh Pardanini MD, Alessandro Vannucchi MD, Srdan Vestovsek MD, Pierre Noel MD, Ruben Mesa MD, Joachim Deeg MD, John Camoriano MD, Susan Leclair MD, Jason Gotlib MD and Joy Selak PhD.

(Ross Levine MD was unfortunately unable to attend due to a snowstorm in NYC, which prevented him from flying to Phoenix; however, he delivered his presentation by phone link assisted by Dr John Camoriano who helped with the overhead slides. Ayalew Tefferi MD was also unable to attend, because he was on jury duty).

Introduction

On February 9th and 10th, 2013 my sister Suzy Whitty and I had the pleasure of attending the Seventh Biennial Joyce Niblack Memorial Conference on the Myeloproliferative Neoplasms (MPNs), presented by the MPN Education Foundation at the Mayo Clinic in Phoenix, Arizona. Prior to the conference, the MPN Education Foundation asked if I could take notes at the conference and share them with those who were unable to attend. The following pages contain a typed record of my hand written notes from the conference, which I typed up after I returned home. To improve readability and to make complete sentences from my abbreviated, and at times cryptic notes, I have occasionally added extra words, which are indicated by parentheses (). I tried to take down as much information as I could and to record the lectures as precisely as possible, however, I apologize for any errors, omissions or inaccuracies my notes may contain. Also, please note, the presenters have provided their slides for viewing on the MPN Education Foundation website at <http://www.mpninfo.org>.

Acknowledgements

Suzy and I enjoyed a whirlwind but very rewarding and informative six-day trip from Melbourne to Phoenix and back home again. Having attended the 2011 conference on my own, (as my husband Mike needed to stay home with our two school aged children) it was a great pleasure to have Suzy's company and moral support on this occasion, and to share the experience and adventure together. We are very grateful to our husbands Mike and Gerry who encouraged us to attend the conference in Phoenix and also thank our children for giving us leave passes to travel to the US and for helping their dad's at home while we were away!

Attending the conference is a great privilege and a wonderful opportunity to learn so much about MPNs. Thank you to the wonderful Haematologists who generously gave up their weekend to share their knowledge, experience and research findings with us, and who availed themselves so graciously by mingling and chatting with attendees during the breaks, at the Saturday evening reception, and by participating in the formal the question times and the disease-specific breakout sessions.

After attending the conference I returned home to Melbourne feeling empowered by the knowledge I had gained. I was inspired by the dedication and enthusiasm of the physician scientists in the US and around the world, who are working tenaciously to elucidate the genetic basis and the pathogenesis of MPNs. This research provides hope that eventually new treatment options will be developed which will lead to better outcomes for MPN patients in the future.

It was a pleasure to again meet up with my fellow MPN patients and friends who I had met at the 2011 conference and also to meet new MPN patients and their loved ones on this occasion. As patients with rare chronic diseases who rarely have the opportunity to meet one another, it was a welcome chance to share experiences, which helps to feel one is not alone, and builds a sense of community. Thank you for the warm welcome Suzy and I received from both the physicians and my fellow MPN patients and their loved ones.

Last but not least, I extend a huge thank you to the volunteer patients and family members who planned and organized the conference, especially Bob Niblack, Antje and Jim Hjerpe, Bob Swanson, David Alexander, Vicki Taylor and Ian Sweet (who unfortunately was unable to make the trip from Australia). Your dedication and efforts in planning, organizing and running the conference, helped to make it a great success.

Friday 8 February: Luncheon at the Copperwynd Resort and Club

The conference began with a delicious buffet luncheon at the beautiful Copperwynd Resort in Fountain Hills, not far from Scottsdale, nestled high on a mountain ridge, overlooking the spectacular Sonoran desert. The energy there was palpable as new and old friends gathered and discussed their experiences with MPNs, before the formal conference proceedings began early on the Saturday morning.

Saturday 9th February, Ruben A. Mesa, MD

(Professor of Medicine and Chair of the Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, Arizona)

Dr Mesa opened the conference with a welcome and a dedication to the conference founders, Joyce and Bob Niblack. Joyce, (who sadly passed away in 2009) was the driving force behind initiating these conferences, and together with her Haematologist, the late Dr Harriet Gilbert and Dr Richard Silver, planned and ran the first Doctor-Patient MPN conference in 1999. The idea of these conferences was to help make a difference for patients afflicted with MPNs, by enabling MPN physician scientists to share their research findings with patients, and to enable patients and carers to interact and meet one another. The conference provides additional tools of:

1. Establishing a sense of community so you do not feel alone.
2. Education. MPNs are complicated diseases. There is a lot of information on the internet and a lot of it is accurate but is it accurate for YOU?
3. This meeting is to complement all that you are already doing and provides more detail than you can get from a brief visit with your own physician.

Dr Tefferi was unable to come to present at the conference because he was on jury duty. Dr Mesa thanked the unrestricted educational grants from Incyte, Sanofi and Celgene, the MPN Education Foundation and Antje Hjerpe, Bob Swanson, Ian Sweet and Bob Niblack and everyone who attended.

Ross Levine, MD - How close are we from understanding the cause of MPNs?

(Associate Professor of Medicine at Weill Cornell Medical School, NYC).

(Dr John Camoriano, (who was also a very entertaining Master of Ceremonies for the conference) assisted with the overhead slides for Dr Levine, who spoke by phone link from New York City, where he was snowed in, and unable to fly to Phoenix for the conference.)

Dr Levine, associate member at Memorial Sloan Kettering Cancer Center in Human Oncology and Pathogenesis Program and Leukemia Services and Associate Professor of Medicine at Weill Cornell Medical College, began by thanking Joyce and Bob Niblack and saying it is amazing what they have done to start these wonderful meetings and he said how wonderful it was to have so many great people presenting to patients on scientific questions and advances in the field.

He discussed the work being done in the Levine laboratory in genetics and targeted therapies in MPNs. He said mutations, which activate JAK2, are hallmarks of all MPNs but the question is, what do the mutations mean and what do we know about JAK2?

The JAK2 mutation is a single position in the DNA sequence where a valine is substituted for a phenylalanine (amino acids). This single amino acid change is found in about 90% of PV patients, 60% of ET/PMF (Primary Myelofibrosis) patients and <10% of ET/CMML patients. This mutation originates in a single blood cell after birth and has the capacity to over-take all other blood cells. Some people with MPNs are JAK2 negative and may have the LNK or MPL mutations however, whether you have the JAK2 mutation or not, the disease is similar and all these mutations result in increased activation of JAK2 and excess proliferation of blood cells.

We now have the technology to do whole genome sequencing to identify MPN alleles (positions on genes) and have done whole exome sequencing on 20 MPN patients who were either JAK2 positive or carry the MPL and have MF or have transformed to AML (acute myeloid leukemia) to try to identify MPN alleles. The lessons to date from this research, is that it is easy to generate the genetic data but it is much harder to analyze and interpret the information. Studies will take months to years to find the real 'drivers' which cause MPNs versus the 'passenger' genes who are present but not the cause of MPNs. The researchers are looking for recurrence of mutations. Many mutations, which are present, may not be specific to MPNs, but are also seen in MDS (myelodysplastic syndrome) and, therefore, they may have a shared biology.

Dr Levine said they hope to find lesions with clinical significance to develop novel therapeutic targets. We are looking for lesions, which predict outcomes, to ensure we aggressively treat patients with poor prognoses and leave patients with good prognoses alone. We want to find lesions, which occur at transformation to AML (acute myeloid leukemia), to be able to prevent or treat leukemic transformation.

We want to know whether there are cooperative somatic mutations, and to understand why although most MPN patients are JAK2 positive, some develop PV, ET or MF (with the same JAK2 mutation). Some mutations are seen in both MPNs and also MDS and AML, but they do not explain the PV/ET/MF conundrum. In some cases *TET2* mutations occur in progression to AML and we also see increases in LDH (lactate dehydrogenase, an enzyme which indicates cell damage or disease).

The Leukemic transformation of MPNs is a challenge we need to do a better job with and Dr Levine is currently working with Dr Verstovsek to learn more about what the genetics of AML looks like. They have learned that *de novo* AML (or AML in people who have never had an MPN) is very different from AML post MPN. In some cases patients lose the JAK2 mutation in post MPN AML and acquire the *TET2* mutation. We cannot think of them (both types of AML) as the same disease. We need to design specific trials for post MPN AML and we want to be ready for the trials with treatments for those patients who need them.

We can measure gene expression that leads to proliferation in MPNs. MPN genes are

very different to 'normal' genes but genes between MPNs are not that different. The predominant gene MPN patients have in common is the JAK2 mutation and it is relevant regardless of the other specific mutations. The Levine lab has done mouse model experiments using JAK2 inhibitors in JAK2 mutant MF mice. They found they can't cure the mice, but the drugs reduced circulating cytokines and improved body weight and they also found that the mice died if the drugs were stopped.

How effective are the JAK2 inhibitors and why doesn't the JAK2 clone go away? Cells acquire the ability to stick around, termed 'creep', and don't die. In some cases the JAK2 inhibitors generate persistent cells, which are insensitive to the current JAK2 inhibitors and re-acquire the ability to activate JAK2. Newer studies are looking at combination therapies with using Ruxolitinib (Jakafi) and HSP90. We need a drug to eradicate the JAK2 mutation and another drug to reduce the reticulin fibrosis. We need to attack it from different angles.

Questions to Dr Levine:

Question: Dosing in AML?

Answer: We need higher doses to avoid resistance.

Question: What is the percentage of PV patients who convert to AML?

Answer: This is a critical question and a major goal for this year is to see if there are predictors.

Question: (RS) If a patient is not responding to Ruxolitinib, will they respond to another drug?

Answer: This is being studied by trying drug A, having a 'drug holiday' for a couple of weeks then trying drug A plus drug B.

Ayalew Tefferi, MD: Prognostication and Management in MPNs: 2013 Update

(Professor of Hematology and Medicine, Mayo Clinic, Rochester, MN.)

(This lecture was presented by Drs Mesa and Camoriano because Dr Tefferi was unable to attend as he was doing jury duty.)

Dr Mesa spoke about understanding MPNs. They are three diseases, which were first described in the 1950s by Dr William Dameshek, who was the first president of ASH (the American Society of Hematology). The annual incidence of MPNs is approximately 1:100,000 in the US.

The natural history of MPNs:

PV/ET/early PMF: Short term risks of blood clots and bleeding.

PMF: Some patients with high platelets actually have early MF. ET patients are not all the same. Some have enlarged spleens and marrow fibrosis, which provides clues in early MF. Some have lower risk of progression and the BM looks normal. ET and PV can

both progress to PET/PPV (post ET/post PV) MF with a variable burden of disease, which includes anaemia, splenomegaly, night sweats, weight loss and progression to AML. We have to remember health is a journey of which an MPN is an aspect. If you are older and have other diseases, you can have more severe problems. If you are generally healthy you may still live as long as you were meant to live.

Discussed an Italian study of 1000 patients with ET, in which a subset really had early MF. It is not easy to predict which patients will progress. ET/PV/MF are a spectrum. In Post MPN MF we see anaemia, the over production of blood cells has gone away. We see reduced blood counts in those on hydrea, and enlarged spleens. They tend to develop symptoms early in the disease. Scaring in the bone marrow is a side effect of the disease, not a symptom of disease progression.

Discussed assessing risk in MPN patients:

High white cell counts increase the risk of vascular events and progression.

Platelets: Low platelets are a negative sign of progression. High platelets >1,000,000 increase the bleeding risk. Have developed prognostic scales which look risks: age, having other medical problems, WCC, HB, constitutional symptoms (weight loss, night sweats) spleen size, bone marrow scaring, previous blood clots.

In ET/PV: the first short-term goal is to prevent blood clots and bleeding.

The long-term goal is to prevent post ET/PV MF and MPN blast phase.

ET management: All should take Aspirin unless contraindicated. (Patients need) aggressive control of cardiovascular risk factors. For high-risk patients, front line treatment is Hydroxyurea (HU) or Anagrelide.

PV management: Aspirin. Reduce cardiovascular risk factors. Hydroxyurea or Interferon are both front line treatments. Studies are currently being done to compare these agents.

MF: Symptoms flow from how the leukemia affects us. The treatment is aimed at decreasing the spleen size and improving blood counts.

We have therapy choices from observing to stem cell transplant. We need to try to balance between options and look at how effective the medication is, transplantation, the quality of the donor, the individual who has to face these choices. The medications for MF used previously have been mainly disappointing and include EPO (erythropoietin), androgens and thalidomide. Splenectomies are only done rarely in MF now. Since 2007 and the discovery of the JAK2 mutation there has been the development of new drugs of which many have been trialed. As well as developing new drugs we need to know how the disease affects you and your quality of life.

Dr Camoriano discussed life style and cardiovascular risk factors. Not everyone needs treatment. High platelets can cause falsely high potassium levels (due to high platelets). HU and IFN reduce spleen size. Androgens increase Hb. (In the future we are likely to see) multiple treatment options and individualized medicine.

Alessandro Vannucchi, MD: Evolving treatments for ET

(Associate Professor of Hematology, University of Florence, Italy)

Dr Vannucchi traveled from Italy to present. He said they have similar patient meetings in Italy for patients to discuss their experiences but Italians find it harder to discuss their health than Americans do.

He discussed chronic MPNs including CML (chronic myeloid leukemia), and the classical MPNs ET, PV, MF (essential thrombocythemia, polycythemia vera, myelofibrosis) and CNL (chronic neutrophilic leukemia), CEL (chronic eosinophilic leukemia), mastocytosis and MPN-unclassified. These disorders are completely different from solids cancers.

ET is the most common of the MPNs. Many patients are young and have issues with pregnancy and thrombocytosis. Many patient experience clinical manifestations, which are often vascular, however most are uneventful. Many patients need no treatment for many years. There are lower rates of transition to MF and AML.

There is evolving knowledge on the diagnostic criteria, issues effecting progression and new treatments. Diagnosis is not simple. It is not just high platelets. It requires four criteria.

1. A sustained increase in platelets >450,000. Essential but not enough on its own.
2. Bone marrow biopsy (BMB). Increased megakaryocytes or a left shift in white cell counts.
3. Not meeting the WHO criteria. If not JAK2 positive, it does not exclude an MPN.
4. A BMB is essential for diagnosis.

Early/pre-fibrotic MF is a differential diagnosis. It is a challenge to distinguish from ET. You can't distinguish ET from PMF (Primary Myelofibrosis) just of clinical examination and blood counts. You must do a BMB (bone marrow biopsy).

PMF: Characterized by a hypercellular marrow compared with aged matches. We see increased granulocytosis, decreased erythrocytosis and dense, loose clusters of megakaryocytes. Survival of Early MF is lower than true ET. Haematopathologists are able to review slides and distinguish between the two different entities. The problem is that it is difficult to distinguish and there is not a universally agreed criterion. Diagnosis is based on very narrow morphological criteria and there is a lack of specific molecular characteristics. There is not much difference in treatment between early MF and true ET and it is difficult to explain and communicate this to patients. (It is more of an issue for the doctors than the patients!) Doctors will usually say to patients they probably have a variant of ET, which will be treated as ET. They are asked to come for appointments every 4 months rather than every 6-12 months as in true ET. ET can evolve into MF in about 10% of patients after 15years. Signs of progression include anaemia, blasts in peripheral blood, splenomegaly (>5cm below LCM, (left costal margin)), and development of constitutional symptoms.

ET is the less interesting of the MPNs. Risk stratification of ET and PV is determined by the risk of clotting and bleeding. High platelets, *per se*, are not correlated with risk of

thrombosis. Extreme thrombocythemia is a risk for bleeding. The doctor can't change age, or life style factors such as smoking and diet. The target of treatment in ET and PV is to reduce clotting risk.

Risk factors for clotting: JAK2 positive, high WCC, inflammation increased CRP (C-reactive protein) and advanced age. Hydroxyurea (HU) is the main drug used. It helps prevent clotting in high risk ET. HU is better than Anagrelide. There is no substantial evidence that HU increases the risk of AML when use as a single agent. HU is usually well tolerated for long periods of time. Some patients convert to AML when they never had HU.

If HU is not working Anagrelide may be used, but it only decreases platelets and it can have cardiac side effects. It is not proven to be better than HU. They are questions in relation to whether Anagrelide may increase transition to PETMF. In the UK and Europe it is only used as second line therapy. In the US it can be used as first line therapy.

Interferon (IFN): Lowers platelets and may induce remission. The conventional formulations are not well tolerated. The pegylated formulations are better tolerated. 40% of patients need to cease IFN due to adverse effects.

Antiplatelet Treatment: There is no formal evidence for the safety of Aspirin in ET. The ECALP (European Collaboration on Low-dose Aspirin in Polycythemia Vera) study showed evidence for use of Aspirin in PV. Aspirin is routinely used in ET. If platelets are >700,000 it is contraindicated because it can cause bleeding.

What is new in MPN treatment?

- We are rethinking Anagrelide and doing a randomized trial with HU and Anagrelide. There is no evidence HU is superior Anagrelide. There are similar rates of thrombosis and haemorrhage and similar rates of discontinuation.
- IFN: trials are ongoing.
- Vorinostat: effective in 30% of patients. No effect on JAK2, 50% need to discontinue due to side effects. We are a long way before we would use this drug.
- Imetelstat: an inhibitor of the enzyme telomerase, which is expressed in neoplastic cells. It is used in patients intolerant of JAK2 inhibitors. It decreases JAK2 but can cause neutropenias, anaemia and increased infections. It is interesting but needs more work. It is administered via IV infusion, so patients have to go to hospital to receive it.
- Phase II trial of JAK2 inhibitors (Jakafi/Ruxolitinib), are under way in advance ET and PV. It is usually well tolerated but can cause anaemia. It causes a prompt decrease in platelets, normalizes white cell counts, reduces spleens, improves constitutional symptoms and has a modest effect on the JAK2 mutation level. It is

not for all patients who have ET. It is OK for some who are refractory to other treatments.

Srdan Verstovsek, MD: JAK2 Inhibitors: Where do we stand?

(Medical Oncologist and Associate Professor of Medicine, Department of Leukemia, University of Texas, MD Anderson Cancer Center, Houston, TX.)

The main problem in MF is to try to suppress the clinical problems of anaemia, splenomegaly, and constitutional symptoms. None of the traditional treatment options have been approved.

The JAK-STAT pathway is important in 'normal' blood production. The JAK2 gene is specifically found in bone marrow cells, not in other cells. It is needed to make RBC and platelets. JAK2 inhibitors block JAK 2 and cause anaemia and thrombocytopenia.

The JAK2 mutation was discovered in 2005. It is an acquired mutation of a gene, which results in a constitutively active JAK2. It causes disease in mice. Not every MPN patient has the JAK2 mutation, however, regardless of other mutations, the problem in all MPN patients is increased activation of JAK2.

The JAK2 inhibitors are not specific for the JAK2 enzyme. They work whether the JAK2 mutation is present or not. They lower RBC and platelets and the effect depends on the dose. We are talking about controlling the disease and living longer and better, not curing the disease. The only approved JAK2 inhibitor in the US is Ruxolitinib (Jakafi). Hopefully we will have more soon, because they don't all work in all patients.

In evaluating a JAK2 inhibitor we look at its ability to shrink large spleens. Ruxolitinib can induce a rapid and durable decrease in the spleen size of patients with splenomegaly, regardless of their JAK2 mutational status, and improved constitutional symptoms such as weight loss. Some patients have done so well they have gained too much weight! Reducing the spleen improves the patients' quality of life. The JAK2 inhibitors do not change the level of fibrosis in the marrow.

If the patient has side effects of the treatment and the treatment is stopped we see a return of the constitutional symptoms within 7 days and the fatigue and weakness return. The key to managing the side effects is to adjust the dose, not stop the treatment.

Can JAK2 inhibitor prolong life in MF? The studies show a better survival in patients given Ruxolitinib, because they have less cachexia and infection. Dr Verstovsek encouraged patients to share their experiences with their doctors and other patients. JAK2 inhibitors can also be used in patients who are waiting for a SCT to improve their chances of surviving long enough to get the transplant.

Richard T. Silver, MD: Is PV curable?

(Professor of Medicine and Director of the Leukemia and Myeloproliferative Center at Weill Cornell Medical College- New York Presbyterian Hospital, Medical Director of the Cancer Research and Treatment Fund, Inc.)

1. A brief history of PV.
2. The types of INFs and their activities.
3. Clinical and molecular results.
4. Conclusion.

Discussed the 20 years Polycythemia Vera Study Group (PVSG) that ran from 1967-1987. During this study patients had different treatments, P^{32} (radioactive phosphorous), chlorambucil and phlebotomy. P^{32} and chlorambucil increased the risk of progression to AML. Those on phlebotomy alone had increased risk of thrombosis and CVA in the first 5 years of treatment then seemed to survive better. With phlebotomy treatment was associated with poor tolerance and a tendency to MF early and increased vascular complications because the disease was not opposed. There were also problems of anaemia. The majority of Haematologists use HU. It is not the drug of choice in Dr Silver's opinion.

General remarks about IFN:

It was discovered 50 years ago. There are three types. PEG-interferon makes the IFN last longer and produces a sustained level. Merck-Schering make PEG-Intron, Roche make Pegasys, (which only requires a once/week dose). There is no evidence of superiority of (between either) the regular interferon and pegylated IFN. It is just a matter of convenience. As the dose is sustained in the blood for longer, you may be able to use a lower dose effectively.

The activities of IFN:

- Specifically affects JAK2 in stem cells in mice.
- Affects intracellular signaling related to JAK-STAT and other pathways.
- Affects stem cells in PV.

Treatment with IFN in PV:

- Must start and maintain at a low dose.
- Requires long-term treatment. To get HCT <45%.

Studies show progression free survival from thromboembolisms in 55 patients. It works on white cells and endothelial cells to decrease risk of thrombosis.

Dr Kiladjian in Paris found a 90% decrease in the burden of the JAK2 mutation and it was undetectable in 24% of his patients. Clonality changes in PV following treatment with IFN can change abnormal mutations and suppress erythroid colonies.

PV is a disease with a broad spectrum of clinical manifestations. The range of phlebotomies required ranges from 1-25/year. Each patient has a different activity of the disease reflected by the phlebotomy requirement. Reasons for differences in disease activity:

- More advance cases.
- Higher JAK2 level/ more advanced disease.

INF is effective in treating the fibrosis in PV, if started early. Experienced Haematopathologists can distinguish between ET/PV/MF. Need to start early (on IFN). Don't wait until the reticulin fibrosis is Grade 3 and collagen is present.

Is PV curable? Eliminating JAK2 is not the answer. Other mutations such as TET2 occur. INF may be the best treatment to control proliferation in PV.

Biological basic for use of IFN:

- Induces haematological and molecular remission.
- INF in combination with JAK2 inhibitors.
- Try for clinical response, not molecular remission to avoid toxicity.

PV is not curable with IFN, but clinical remission is possible and attainable and quality of life can improve.

We should treat earlier rather than later. If so, we can get reversal of fibrosis and normal marrow architecture. Early means MF Grade 1. We don't wait to treat diabetes until the patient is in a coma and we don't wait to treat lung cancer until the disease is metastatic. If we wait to treat with INF until the MF is advanced it may be too late.

Panel of doctors:

Question: Can niacin lower platelets?

Answer: It can lower cholesterol.

Question: Does the presence/absence of the Philadelphia chromosome have any relevance in MPNs?

Answer: CML is one of the MPNs. It has a specific mutation, the BCR-ABL mutation. It is one of the few cancers with a specific mutation, and which has a drug, Gleevec, which works with minimal toxicity. It is one of the great achievements of the 21st century. We thought the JAK2 solution would be to develop another Gleevec like drug. However, the MPNs (ET/PV and MF) are much more complicated diseases than CML.

Question: Why do some patients convert from ET to PV or were they PV in the first place?

Answer: Conversion is possible. ET can have different phases. It may have an increased JAK2 level over time. Sometimes it is not clearly diagnosed in the first place.

Question: High white cell count and ET?

Answer: There may be a prognostic role of having a high WCC. We don't have clear evidence from trials yet.

Question: What are the indications for starting JAK2 inhibitors in MF?

Answer: Risk assessment for survival. If there is organomegaly and symptomatic

disease we should use them. They shouldn't be used if there are no symptoms or only anaemia. If the patient had a big spleen, weight loss and anaemia, they would have a good chance of reducing their spleen, increasing weight and improving QOL.

Question: After a splenectomy, what takes over the blood cell production?

Answer: We do not leave in a spleen that is very large for the purpose of blood cell production.

Question: Does previous treatment with IFN have any effect on the success with SCT?

Answer: No adverse effects of IFN on transplant outcomes.

Question: How often should you have a BMB?

Answer: What do we learn from a BMB? The level of scarring; chromosomal changes, how the BM looks, and the presence of blasts or normal cells. A BMB should be done at diagnosis, as a baseline. It can be repeated to check for signs that the treatment is improving the disease. Whether or not to do a BMB is individualized. Those who enroll in clinical trials may have a BMB done more often for research purposes.

Question: How do you know if you have other mutations? Is it important to know?

Answer: The JAK2 mutation is the sentinel mutation. PV has lots of overlaps with ET. Patients can have high platelet counts or high white cells counts. Having a high platelet count can be reactive. We need to use clinical signs and lab tests. TET2 is one of the many mutations seen in MPNs. There are many other mutations but at present they are mostly of research interest. High MPL and high platelets can indicate ET. With time, we might have a better understanding of what other mutations mean.

If you have a good ET diagnosis with modern treatment, your life expectancy is as good as normal controls. The role of mutations is quite important in MF where there is a lot of genetic instability.

Question: Have the studies looked at ruxolitinib and other combinations of drugs?

Answer: The trials didn't allow for combinations. If a patient (man?) on a trial develops anaemia, testosterone can help some patients. There is no evidence from studies; it is all from clinical use.

We shouldn't combine medications if there is a risk of toxicities. A small subset of patients may get high platelets and high WBCs and ruxolitinib may not be enough (to control blood counts). HU is not a great drug in MF, but it can reduce counts and has been used.

The more combinations we use the more we will learn for future patients. Ruxolitinib is only the first JAK2 inhibitor. In oncology we see 2nd, 3rd, and 4th generation drugs, which are often better at controlling counts. We will learn from these in the future. (S.V). We may use Pegasys plus Ruxolitinib.

Question: Use of resveratrol as a supplement.

Answer: The utilization of diet may be very helpful such as an anti-inflammatory diet like the Mediterranean diet with lots of fruit and vegetables, whole grains and minimal meat; or a vegan diet. These diets lower CRP (C-reactive protein, an inflammatory marker) and reduce vascular events.

In the US, once a drug is approved for one indication, it can be used for other diseases. Pegasys was approved for Hepatitis C, but doctors can appeal to insurance companies to use it for other conditions, if studies show efficacy. The drug companies generally need three peer reviewed published journal articles to approve cover for a drug. In cancer treatment, 50-60% of cancer drugs used are off label (not approved specifically for that disease).

In Europe, Pegasys is approved in some countries but not in others. It is of no value in advanced MF. It also has side effects of depression, autoimmune problems and cardiomyopathy.

Joachim Deeg, MD: Transplantation of MF: For whom, when and how?

(Professor of Medicine, University of Washington, Member of the Fred Hutchinson Cancer Research Center, Seattle, WA.)

Why transplant in MF? MPNs (PMF, ET and PV) cause MF and are diseases of the bone marrow. In PMF, (the question is) can we get the stem cells to graft and allow the bone marrow to rebuild?

Risk factors have been developed for high-risk transplant patients:

Anaemia, WBCs >25,000, myeloblasts, age >65yrs, and constitutional symptoms.

If a patient is in the high-risk group, we have to consider whether it is worth taking the risk (to undergo a transplant). Other risks, which are not included in the current stratification include:

- The severity of fibrosis. Is it in other organs?
- Spleen size and portal hypertension. It takes longer to graft if the spleen is enlarged.
- Duration of the disease.
- Mutations. Additional mutations impact on transplantation (success).

(We need to) look at the patient and disease characteristics. Every patient considering a transplant needs to have HLA tissue typing done. The results with an unrelated donor are indistinguishable from a related donor. Differences in outcomes are more related to risk classifications before and after transplant. Large spleen size and duration of the disease decreases immune function (and transplant outcomes). Patients with lower risk classification have higher survival rates after transplant.

Causes of death after transplant: Relapse, GVHD (graft versus host disease), infection, multi-organ failure, graft failure/rejection, secondary cancers, and intracranial hemorrhage.

Overall survival by year: In more recent year (we) have transplanted patients in high-risk categories. (I) Never talk a patient into having a transplant. I say, "if you are considering a transplant, this is the time to proceed." (What is the) survival of HCT (hematopoietic stem cell transplant) by JAK2 mutation? We are not sure yet.

Conditioning regimes (for SCT):

Low intensity regimes carry a risk of not completely eradicating the disease.

Overall survival by age:

The oldest surviving patient was a 78 yr old retired orthopedic surgeon.

Problems: GVHD. (The risk) is lower if using statins (anti-inflammatory).

Organ toxicity

(We use a) decision tree (to decide who is likely to be successful in transplantation).

Summary:

HCT offers an effective curative treatment of MF. Follow-up shows patients surviving up to 20 years and few relapses.

Ruben A. Mesa MD. What can we expect from our MPN therapies?

(Professor of Medicine and Chair of the Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, Arizona)

What is the spectrum of the disease burden of having an MPN? What phenotype clusters do we see in ET/PV/MF?

ET – Has the lower risk of progressing to MF.

PV – The likelihood of progressing to MF is very real

ET/PV

- Carry macrovascular risks (of clots in) arteries and veins.
- Microvascular risks – migraines and floating spots.
- Erythromelalgia – (episodes of pain, burning, redness in the extremities)
- Difficulty concentrating without phlebotomy.

MF

- Cytopenia - anaemia and fatigue.
- Enlarged spleen. Can feel (spleen) in ET and PV but it is not usually problematic. It is an innocent bystander.
- Can have (splenic) infarctions.
- Mechanical problems (due to enlarged spleen)
- Fatigue.

(We looked at) risk of blood clots in MF and symptoms in 1197 MPN patients. (We found blood clots are) not necessarily dependent on blood counts and are very common.

Severity of constitutional symptoms:

- More common in MF
- Itching in PV
- Issues with intimacy and mood.
- In MF patients, symptoms are as severe as in solid tumours.

In ET and PV there are symptom clusters. Within ET there are four distinct clusters of patients.

(We have) evolving MPN prognostic scales. Some patients with MF can live a long time.

PV risk: increased symptoms, increases risks.

High risk MF tends to have more symptoms.

Quality of life in patients: Issues.

- Symptoms, itching.
- Related to medication toxicity
- Complications such as CVA.
- Stressors: financial, emotional, intrapersonal.
- Comorbidities.
- The hassle of medical care.

What are we trying to achieve?

- Prevent a blood clot
- Delay disease progression
- Prolong life

Ruxolitinib Phase III trial - symptom response. Patients felt better on Ruxolitinib, but not on the Placebo. In P. Vera it can give symptomatic benefit, but can be disappointing as well. The dosing and dose optimization is important.

(Questions to investigate) Can using JAK2 inhibitors slow progression? Does delaying treating increase the risk of progression?

Conclusion

- The symptomatic burden in MF is a real issue.
- There are distinct symptom clusters.
- Improving symptomatic burden is an appropriate and achievable goal of treatment.

“The spleen is an organ of contradiction and mystery: in health of relatively unimportant function, in disease a menace of grave import.”
- Dr. Will Mayo

Susan Leclair, MD: Common MPN laboratory questions.

(Chancellor Professor, University of Massachusetts, Dept. of Medical Laboratory Science, Dartmouth)

Once upon a time, physicians knew all the answers and patients believed them. Not so any more!

- It used to be that you got a diagnosis, you cry, you go the church/temple etc., you take medications and do what your doctor says.
- Now days, you get a diagnosis, you cry, you go online, you go to the '*roots and berries*' you argue and ask 'why'.

Physicians speak in *Medicalese* and only rarely speak in English, so you have to learn to speak *Medicalese*.

It takes two to miss-communicate

Patient Words:

- Fine = I don't want this to be bad so you wont mind if a miss a few salient points.
- Not bad = It really hurts like hell but I am supposed to be brave (male).
- Or: it really hurts but I know no one pays any attention to my complaining about pain so why tell (female).
- I didn't tell him because he didn't ask = you're the hotshot; go figure it out without me.

Physician words:

- Fine = It's not a surprise to me so I don't need to explain it to you.
- Let's repeat it in a few weeks = I'm not sure why this is here so let's hope it goes away.
- That's my job = I can't explain this in English!

Translations: What is *JAK-STAT*? Original name: *Just Another Kinase*

- The *Janus Kinase Signal Transducer and Activator of Transcription* (JAK-STAT) pathway mediates signaling by cytokines, which control survival, proliferation and differentiation of several cell types.
- Constitutive JAK activation lead to persistent activation at STAT transcription factors.
- JAK2 is the gene that turns on a series of actions that controls the production of blood cells and fibrocytes.
- When abnormal, control is lost and excessive numbers of blood cells are produced.

Under *normal* physiological circumstances, when a ligand (such as EPO) binds to a

receptor, a conformational change occurs. The JAK2 protein makes contact with the cytoplasmic receptor, where it catalyzes tyrosine phosphorylation, leading to activation of the *signal transducers and transcription* (STAT) molecules.

When erythropoietin (EPO) binds to the receptor control by JAK2, the cell becomes committed to making red blood cells. If less EPO, few RBC should be made. But with the JAK2V617F mutation, the STAT enzymes are always on, causing more blood cells to be made, regardless of the amount of EPO.

Over time, the mutation causes damage to granulocytes, platelets, and fibrocytes.

One more language: The US will not follow the international system of concentrations and values.

- US (really old): 5000cells or 5K/cm³
- US (medium old): 5.0/10³/μL
- Rest of the world: 5.0/10⁶/L

My spreadsheet or *my precious!* (What to record and track)

WBC: total number of white blood cells

- Can bounce around within +/- 3.0 range
- The neutrophils can double if: fever, exercise, and emotional stress.
- WBCs are suppressed by lots of cardiac meds such as ACE (angiotensin-converting-enzyme) inhibitors (such as Captoril and lisinopril, used to treat hypertension) so don't ever let anyone say to you that things can't be connected.
- Have blood drawn at the same time of day each time, to keep the pre-analytical stuff as consistent as possible.

As MPNs progress, WBC can wander erratically higher. The clinical significance is hard to define as it can bounce so easily. If higher than 3.0x10³ out of the reference range, it is worthy of note.

There are two ways to describe the different WBCs:

- Percentage: Older form. Identifies the first 100 cells and makes great comments on quality.
- Absolute: Identifies 10,000-50,000 cells. Variable on quality, superb on quantity.

Follow neutrophils, as are they are controlled by the same cell (common myeloid progenitor cell) as RBCs. No immature cells should be seen although the occasional intermediate form (metamyelocyte) can be tolerated.

Therefore, follow WCC and Neutrophils.

Reference intervals: 95% of the population is in this area.

Reference ranges:

- Change by method
- Are the dart board
- You want the bulls eye "you"
- Haemoglobin /Hb

You can count RBCs but no one takes that value seriously any more. There are better tests.

Hb= the concentration of oxygen carrying protein

- Can quantify the Hbs who have oxygen and the Hbs that do not (carboxyhemoglobin).
- Hb remains consistent, regardless of cell size.
- Hb varies by gender, age and altitude. If I were in Colorado Springs with an Hb of 14g/mL it would increase.

Signs and symptoms of anaemia:

- ~10g/dL or 100g/L
- Pallor, shortness of breath, fatigue etc.
- Below 8g/dL or 80g/L: Lack of O² damages organs so will usually need a transfusion.

Hb issues of overproduction: More cells make blood more viscous.

“Like Jello™ with lots of fruit versus clear Jello™!”

Hb >14 in women and >15 in men:

- Increases blood pressure→kidney damage or CVAs
- Increase cardiac stress→heart attack
- Increase fragility of blood vessels
- Best indicator of phlebotomy need.
- It is harder for the heart and muscles to work.

Haematocrit (HCT). Once upon a time it was the most accurate test in a clinical lab. Now we don't perform it, we calculate it so it is not as accurate or reliable a measure.

HCT (% RBCs in the blood) is calculated from the MCV (average red cell size).

If you know the average size of the cells, MCV x RBC count = HCT

Hb only makes sense, if all the cells are the same size. As the RDW increases (red cell width) and the MCV decreases, it gets fuzzier.

When the RDW is >20, the HCT is invalid, so using Hb is the most consistent value. Therefore, use Hb if the RDW is high. BUT- if you phlebotomize someone you make them Fe deficient, so the RBCs are smaller and don't live as long and you also get an increased number of smaller platelets.

What to follow on your own spread sheet:

	WBC	ANC	Hb	MCV	MCH	RDW	Plts	Uric acid	LDH/LD
	Ref. Interval	Ref. Interval	Ref. Interval	Ref. Interval	Ref. Interval	Ref. Interval	Ref. Interval	Ref.inter	Ref.Inter
Date	Value	Value	Value						

Hb will be lower in the evening than the morning (up to 1g/mL), due to changes in hydration levels, so have blood drawn at the same time each time.

Chemistry Values:

Uric acid:

- Waste from protein or nuclear metabolism, that must be cleared by the kidneys.
- Too much: causes gout, kidney damage and joint pain.
- Keep diet consistent. High protein meals increase uric acid concentration in blood.

LFTs (liver function tests)

LD (LDH = Lactate dehydrogenase)

- Every cell has this enzyme. When cells are damaged it is released into the blood stream.
- An increase suggests cell damage but use cautiously when on medications.

Bilirubin:

- (indicates) liver damage or hemolysis (RBCs bursting)
- AP (Alkaline phosphatase) = bone, liver or GI damage
- ALT= liver damage (enzyme found only in liver cells)
- GGT= another liver enzyme, but Aspirin can cause it to increase.

If hemolysis (look at) reticulocyte count

If immunosuppressed, (look at) proteins, especially immunoglobulins (use serum protein electrophoresis to measure the different proteins present).

PV Break-out: Dr Richard Silver, Dr Amanesh Pardanani, Dr Pierre Noel.

Discussed management with splenomegaly, when to start cytoreductive treatment, anaemia and phlebotomy, measuring Hb versus HCT in monitoring PV status.

R.S: Discussed use of IFN in MPNs. Side effects are dose related. Always starts on a low dose (because they are chronic diseases and need long term treatment). Start on 2-3MU/week IFN or 45-90 mcg/week Pegasys. Dr Harriet Gilbert first used IFN to treat MPNs. Some patients had a clinical response that lasted 3-4 yrs. Contraindications for IFN: severe autoimmune diseases: Lupus, Rheumatoid arthritis.

J.G: IFN dosing – use lower dosing and frequent dosing. Most PV pts in the US are not on IFN. Pts on (high) CML doses (of IFN can get) significant depression. Even low doses can cause depression. (There is the feeling of) uncertainty of being on long term chemotherapy. Older patient don't want to be on IFN (due to side effects).

R.S: If >10 phlebotomies/year = active disease. PV is a progressive disease. MF is the natural progression of untreated PV. Megakaryocytes cause fibrosis. Patients in their 40s shouldn't be on HU. R.S. said there has been no comparison of HU and IFN in a trial. (He has treated) many patients with IFN and has had no incidence of AML in these

patient. IFN has never been shown to be leukemogenic.

Pipobroman in PV: A potent marrow suppressant.
Pipobroman: 10% AML in 10yrs; 18% AML in 15yrs
HU: 15% AML in 15yrs

The FDA didn't allow Pipobroman in the USA. HU is leukemogenic. Never allow a younger patient to take it. It causes squamous cell carcinomas in 20% of cases. Even high doses of IFN do not cause AML. It is a natural biological product.

Question: treatment for 58yo PV patient, WBCs 23?

Answer: If low thrombotic risk. (no Hx of thrombosis) HCT <42% for Women, <45% for men.

High risk of thrombosis: high WBCs, high platelets. Treat patients earlier to lower risk to prevent them from becoming high-risk patients: platelets/endothelial cells/WBCs all interact. ↑ clotting risk.

Question: What should a patient look for (to indicate) conversion to MF?

Answer: ↑ spleen, ↑ WBCs, ↑ LDH, indicates ↑ cell turnover. We get concerned if the doses of HU needed to control the counts decrease. If you have hypertension you have high risk (of thrombosis). The risk doesn't reduce immediately when blood pressure is controlled.

Question: In someone with PV who has ↑ spleen, when do you start Ruxolitinib?

Answer: Ruxolitinib is very good at ↓ symptoms, bone, pain, spleen size, itching. If symptomatic splenomegaly, it impacts quality of life.

Chlorambucil: Alkylating agent: causes AML. Use of phlebotomy only, used to be thought to be better. It activates platelets and increases clotting risk.

The reason HU is used is to suppress bone marrow. It suppresses RBCs, WBCs and platelets. If you allow the spleen to become very big the bone marrow becomes osteosclerotic (scarred). You don't want to let the spleen get bigger and bigger. There is a diversity of opinions (among physicians) on when to start cytoreductive treatment. HU or IFN may change to natural progression of the disease. Not all doctors agree on this. Can't do parachute studies (leave some patients untreated/ exposed to known risks). Phlebotomy only increases platelets. Can't buy HU in Scandinavian countries. Can't buy IFN in Italy.

Question: What is the best indicator of PV status, Hb or HTC?

Answer: HCT won't be accurate in PV because it is a derived value. Use RCC.

Question: what is the significance of low cholesterol levels in MPNs?

Answer: In MF it is an indicator of advanced disease with ↑ spleens. Low cholesterol is seen in other malignancies too.

We don't know if the level of JAK2 will change to course of the disease. PV may be a more JAK2 driven disease. Jakafi (Ruxolitinib) is approved (in the US) for MF.

Question: For a patient with PV how long can you be on Pegasys?

Answer: They have not been) a large number of patients who have been on IFN for longer than 20years.

We see a reduction or elimination of the JAK2 allele burden. There is no information on whether ↓ the JAK2 = remission of disease. We are not sure what it means. It is not like CML (where we see) a ↓ in the CBR-ABL mutation.

Question: What is the percentage of patients who convert to AML?

Answer: In general, 10-20% over 20 years.

R.S: This is a gross understatement. Not all patients have been studied. If you follow patients long enough, all will get MF. It is part of the disease. MF is related to ↑↑megakarocytes. Don't wait until your house is burnt down to call the fire brigade. Call the fire brigade when it is just smoking!

P.N: We are hopeful IFN will delay progression.

In bud chiari syndrome (portal vein thrombosis) we should phlebotomize to <33% HCT. Aim for 38-39% HTC in women.

There are no absolute answers in medicine. It is subjective. All patients want absolute answers. But doctors can't do that. It also depends on where you are in the course of your disease.

Surgery: Women, aim for <42% HCT, platelets <400. Men <45% HTC and Platelets <400. Use a prolonged anticoagulant ((35 days)

Question: Transitioning between IFN and Pegasys.

Answer: Delay withdrawal of HU until Pegasys has started to work. HU has a short half-life of 2-3 days.

Question: If a patient has a strong family history of depression, is IFN contraindicated?

Answer: The dose of IFN used in MPNs is much lower than what was used in CML. (Most) will respond to (low dose) SSRIs.

Question: What is the dose of IFN needed to eliminate JAK2?

Answer: It's a question of duration. There is no rush!

Sunday, 10 February 2013

Aminesh Pardanini, MBBS, PhD: New Treatments for MPNs- beyond JAK2 Inhibitors

(Assistant Professor of Medicine and Hematology, Mayo Clinic, Rochester, MN)

It is patient conferences that inspire and educate me the most. Thanked Joyce Niblack. Thank you to family and friends. Thank you for furthering our research and enabling us to identify new things and make new discoveries. What is new in MPNs in 2013? What is new and what have we learnt? There are various new drugs, new trials.

The chronic myeloid malignancies overlap:

- Myelodysplastic syndromes (MDS): normal or low blood counts. The maturation sequence is abnormal. Opposite of MPNs. Absence of cytois.
- Myelodysplastic/myeloproliferative overlap: CMML/aCML/RARS-T/MDS/MPN-U Monocytosis/granulocytosis/thrombocytosis/eosinophilia/mastocytosis)
- MPN: CML/ET/PV/PMF/CN/SM,CEL,MPN-U: Hyperactive bone marrow. Increased peripheral blood counts/erythrocytosis.

What is new in PV? At the ASH meeting in Dec 2012 (we discussed how) we have come a full circle in 30yrs. Life expectancy is not ideal. It should be the same as matched controls. There is an 80% survival in 10yrs. Life is threatened by complications: CVA, TIA, risk of burning itself out →MF, scar tissue in the bone marrow. →→→ Risk of AML.

PV Risk Stratification

↓ risk of thrombosis. ↓Risk of MF or AML (modest goals at this point).

- Low risk: age <60, No Hx thrombosis.
- High risk: >60, or Hx thrombosis.
- Low risk with extreme thrombosis: platelet millionaires! >1 million/cmL
- Use ASA (aspirin) in PV to ↓ risk of blood clots.
- In high risk patients, consider HU

Historically: 1978 paper showed a direct correlation between HCT and blood clots.

- ↑HCT = ↑ risk of blood clots.
- If HCT is ↓ to normal range, ↓ risk of blood clots by 4 fold.

The HCT should be <45%. Over time we have lost sight of this with the focus on reducing cardiovascular risk factors.

In Dec 2012 at the ASH meeting in Atlanta, they discussed a study looking at what is the optimal HCT. The standard arm (of the study) aimed for a HCT <45% and the experimental arm had a HCT of 45-50%. Patient with a HCT of >45% had an increased risk of thrombosis and death compared with those with a HCT <45%.

Take home message: Aim for a HCT <45%, especially if you have high-risk disease (increased risk factors for thrombosis). In women with PV, HCT should be 42% or lower.

Low dose ASA. I use HU as first line treatment in pts who don't respond. It can cause severe GI problems or ulcers. In patients refractory to HU, I use IFN in younger patients and Busulfan in older patients.

HU vs Ruxolitinib

Primary end point: to be venesection free and to reduce enlarged spleens in 32 weeks. Symptom relief for patients on HU (responding but still having symptoms, ie pruritis, night sweats etc). Patients were randomized to treatment or placebo or HU and Placebo. The goals: freedom from Phlebs, symptoms, splenomegaly, thrombosis, MF and AML.

PV/MPN: are a marathon (long term treatment of the disease).
Clinical Trials are a sprint, (only) 1-2yrs.
Trials look for: ↓phlebs, ↓splens, improvement in blood counts.

Challenge your doctor. Can clinical trials improve endpoints?

What is new in ET in 2013?

It is essential to have a BMB done at diagnosis (WHO criteria). There are several diseases, which are close cousins of ET, so it is essential to distinguish between them. Early stage prefibrotic MF can present like ET. Patients with true ET have good outcomes. 1% risk MF/AML/yr. Life expectancy is the same as normal (non-MPN) life expectancy. If your doctor makes an accurate diagnosis, the outcome is very good, but you can still get lots of symptoms.

New drugs. If patients are doing well with ET, do they need new drug? Discussed the development of the International Prognostic Scoring of Thrombosis in WHO-Essential Thrombocythemia IPSET- Thrombosis

Which patients will receive HU or IFN in addition to age and previous thrombosis we look at cardiovascular risk factors and presence of the JAK2 mutation.

Now have 3 risk categories. Age, CV risk and previous thrombosis.
In the next few years might change the treatment of ET. If >60yrs, no CV risk factors, no thrombosis: used to treat with HU. Now we might just treat with ASA.

New drug: Imetelstat rapidly induces and maintains substantial hematologic and molecular responses in patients with essential thrombocythemia (ET) who are refractory or intolerant to prior therapy: (pts who failed HU and IFN). Preliminary phase II results:

Imetelstat shuts down the enzyme telomerase. Competitively binds to RNA template of telomerase. Upregulated telomerase may be centrally involved with proliferation and replicative immortality of neoplastic progenitor cells. Imetelstat has a long half-life in bone, liver and spleen.

Inhibiting telomerase, therefore, seems to be an attractive approach for treating patients with ET.

Imetelstat is administered via IV infusion; therefore patients have to go to hospital to receive it. (Not so convenient for patients)

Study looked at patients who had failed all other treatments. The aim was to see what proportion of the patients had normalized platelet counts with the treatment.

Results: 100% of patients had a haematological response of ↓ platelets. (14pts). 92% had a complete response, 8% had a partial response. All pts had ↓ JAK2 mutational level.

This suggests, that unlike HU and like IFN, this drug may have an effect of the mutant clone. Imetelstat was generally well tolerated. It is important that this drug is shown to be

safe because (it will) be used to treat patients for the long term.

Take home message: Let's keep in mind the new model of risk stratification for own practices. Imetelstat is an interesting new drug that is worth examining in polycythemia vera and myelofibrosis.

Randomized Trial of Pegylated Interferon Alfa-2a Versus Hydroxyurea in Polycythemia Vera (PV) and Essential Thrombocythemia (ET). Looked at high-risk pts. Primary outcome measure – to compare the haematological response rates over 4 yrs.

Talked about MF: a triad of misery; anaemia, splenomegaly, cachexia, constitutional symptoms and shortened life expectancy. 15-20% of pts are transplant candidates. Non-transplant option; Ruxolitinib. The first JAK2 inhibitor, (to be approved) but not the best. New drugs might be better.

The current treatment options for MF:

Transplant options – Myeloablative

– Reduced-intensity • Non-Transplant options

– Treatment for anemia

- Erythropoietin
- Corticosteroids
- Androgen + Prednisone
- Danazol
- Thalidomide + Prednisone
- Lenalidomide– Treatment for splenomegaly • hydroxyurea • splenectomy– Treatment for extramedullary hematopoiesis
- Low-dose irradiation – Supportive care.

JAK2 inhibitors are *NOT* JAK2 specific. Affect all the JAKs. Still limitations. The primary benefit is to reduce spleen size but it doesn't last. As soon as pts come off the drug the spleen enlarges again. They also ↓Hb and this results in transfusion dependence. The concern is we are not sure whether the JAK2 inhibitors modify the disease or reverse the fibrosis or make the JAK2 clone go away. We will have to find out about this.

Is combination treatment in our future?

1. The future treatment for MF may more resemble multiple myeloma. (drug cocktail) and less like CML treatment (targeted monotherapy).
2. (There is) concern of overlapping toxicities with combination therapy.

Anaemia is a big problem in MF and = worse prognosis. Dr Tefferi published a study from Mayo Rochester in 2012, looking at 1000 pts. with MF. We need a treatment to reverse this and JAK2 inhibitors don't do this.

Thalidomide: helps anaemia, but worsens neuropathy.

Lenalidomide: helps anaemia.

Pomalidomide: 27% response with anaemia. 3 adverse factors: JAK2 Neg, spleen >10cm, circulating blasts. If patient did not have these adverse factors, they did better on Pomalidomide.

Pomalidomide conclusions:

- Significant erythropoietic activity in a select group of MF patients.
- No definite additive effect of prednisone
- Sensory neuropathy is observed.
- Myelosuppression is less frequent at lower doses.
- Anemia response is durable.
- Does not favorably impact either splenomegaly or myelofibrosis.

Jason Gotlib, MD, MS: Is my MPN Inherited?

(Associate Professor of Medicine (Hematology) Director, Stanford MPN Center Director, Hematology Fellowship Program Stanford Cancer Institute Stanford, CA. Disclosures: Unpaid advisor to **23andme** genetic study on MPNs.)

What are the factors contributing to why I got an MPN? Coronary artery disease (CAD) is multifactorial: acquired genes, family history, acquired risk factors (smoking, diet, hyperlipidaemia, hypertension, inactivity etc). When we talk about family history (Hx) are there changes in genes from our parents that contribute to ↑ the risk of CAD?

In Alzheimer's disease (we know) genes are involved. There is also family Hx. Boxers acquire a type of Alzheimer's from head injuries. Nicotine may ↓ the risk of Alzheimer's (observational studies). There may be other risk factors as well.

There are two types of CAD:

Early onset: 40s and 50s. Lots of genes (involved). <3% of cases. The genes ↑ the likelihood of getting CAD.

Late onset: inherit an ↑ susceptibility. Odds ratio 3-4 x. Lower risk than early onset Alzheimer's Dx.

With MPNs:

- Acquired genes.
- Inherited predisposition.
- ? Environment.
- ? Other factors (yet to be identified)

Acquired gene mutations (in MPNs):

- CML: 100% have BCR-ABL mutation
- PV: 95-98% have JAK2, others have EXON 12.
- ET: 50-60% have JAK2, 1-5% MLB515
- PMF: 50-60% JAK2, 5-10% have MPN515
- Mastocytosis: 80-90% have, KITD8116V

A lot of other mutations are found in the acute phase of the disease. In the blast phase, other genes show up. They are all acquired mutations.

We have 46 chromosomes, 22 pairs and XX (female) or XY (male). We acquire

mutations in genes within chromosomes. 20,000 genes. 3 billion letters make up the full genetic code. (It only takes) a change in one letter of the 3 billion letters (to result in a mutation that changes how the gene functions).

A Swedish Registry Data found the risk of MPN in ~25,000 first-degree relatives of 11,000 MPN patients was 5-7 fold higher than in first-degree relatives of normal individuals.

Therefore, if we inherit a predisposition (of developing an MPN) we have a 5-7 fold ↑ risk of developing an MPN.

Why is there an increased risk in relatives of MPN pts? There is an inherited variation in the JAK2, which is not acquired.

There are two hypotheses for MPN development: (46/1 JAK2 Haplotype & Predisposition to JAK2 V617F+ MPN)

“Hypermutability” theory: the inherited variation causes acquired JAK2 V617F mutations to preferentially arise on the same copy of the JAK2 gene.

“Fertile ground” theory: The V617F mutation rate is the same in each copy of the JAK2 gene; however, in cells in which the V617F mutation lands on, the copy with the inherited variation gains a selective growth advantage.

However, there is no association between 46/1 haploid and either clinical features and outcome (in): age, disease duration, white cell count, Hb, platelet count, EPC, spleen size, survival, arterial or venous thrombosis, hemorrhage, transformation to myelofibrosis or acute leukemia

Therefore, there is no currently role for screening of JAK2 46/1 haplotype in routine clinical practice or knowing whether the disease will develop over time.

To put the JAK2 46/1 haplotype into perspective, the average MPN incidence is 2:100,000. The incidence of MPNs with the JAK2 46/1 haplotype is 4-6:100,000. Therefore, the absolute risk is still very low.

Familiar (inherited) MPNs are exceedingly rare. JAK2V617I mutation leads to ↑platelet counts and a 50% of developing this acquired mutation, however it has only been seen in a handful of families.

23andMe Myeloproliferative Neoplasms Research Initiative is a collaboration between and Stanford University School of Medicine, Memorial Sloan-Kettering Cancer Centre, NY and Mayo Clinic AZ.

Recruitment was on-line and individuals submitted saliva samples and filled out on-line questionnaire on their diagnosis and treatment. Participants provided informed consent and participation was free. The goal was to recruit 1000 MPN patient samples.

They obtained 871 MPN patient saliva samples, between August 2011 and September 2012. (Subjects were) 70% male, 30% female. Median age, 55 (Range 2-87). The self-reported JAK2 status in the ET/PV/MF cases was 49% JAK2 Positive, 13% JAK2 Negative and 38% JAK2 status unknown.

~65,000 controls who were customers enrolled in the *23andMe* Personal Genome Service between January 2011 and September 2012. They were unrelated, mostly European ancestry, male/female %58/42. Median age, 46yrs (range 1-112).

They found the *TERT* (telomerase reverse transcriptase) variant is associated with ET, PV, and PMF. There was no association between the *TERT* variant with JAK2 V617F mutational status.

TERT and MPNs:

In normal cells, progressive shortening of the ends of chromosomes (telomeres) is one mechanism that limits the ability of cells to divide forever.

TERT is a component of (the enzyme) telomerase (telomerase reverse transcriptase), that modifies the ends of chromosomes to maintain their stability.

Cancer cells over-express TERT and ↑ chromosome stability. Some cancer cells may acquire the ability to divide without limit.

We don't know the mechanism by which variations in the *TERT* gene contributes to an increased predisposition to MPN or other cancers.

Therefore, there are inherited characteristics in genes that increase the predisposition of developing an MPN.

How did I get my MPN? Did I inherit a predisposition? Was it due to environmental factors? Did I acquire gene mutations? All these factors may work to increase the risk of developing an MPN. We need (to do) a lot more science before we can find out how these factors work together. The acquired JAKV617F is also found in some people without a known MPN.

Summary of the *23andMe* collaboration

- Germline variations in *TERT*, a gene associated with other cancers, is a new predisposition allele for classic MPNs.
- The *TERT* gene is associated with an increased risk of MPN, regardless of V617F status.
- MPN development is linked with telomerase and maintenance of chromosome stability.
- The JAK2V617F was detected in saliva from MPN patients and from control individuals in the broader 23andMe community.

- What do we do with people who are JAKV617F ⁺ but do not have a MPN? We refer them to a Haematologist.
- *23andMe* plan to return JAK2 V617F findings to the control participants with education about test results, recommendations for follow-up, and validation of V617F status by standard blood testing.

Pierre Noel, MD: Issues of Clotting and Bleeding for MPN Patients.
 (Professor of Medicine and consultant Hematologist, Mayo Clinic, Arizona)

In medicine, things that make a lot of sense are not necessarily correct.
 More questions...few answers! What is the scope of the problem?

Thrombosis:

- PV: 12-39%
- ET: 11-25%
- MF: 10%

60-70% arterial thrombosis. Splanchnic and cerebral.

Bleeding:

- ET: <10%
- PV: 10-15%
- MF: 15-20%

Why we clot excessively? (The platelet count doesn't correlate with clotting risk).

- increased platelet activation,
- ↑ Hb,
- ↑ WBC,
- JAK2 allele burden,
- Inflammation: CRP, Pentraxin 3,
- decreased protein S,
- Abnormal lining of blood vessels (endothelium)

Why do we bleed excessively?

- decreased platelet granules.
- Abnormal platelet aggregation.
- Increased breakdown of Von Willebrand molecule: related to high platelet count.

(What is the) spectrum of management? Dr. Tefferi: (favors) HU; Dr. Silver: (favors) IFN – standard of care. The truth is probably somewhere in the middle.

Aspirin: (ASA) works by binding to cyclooxygenase-1 (COX-1) on platelets and reducing production of thromboxane A2. (To prevent excessive clotting)

Primary prevention: Low dose Aspirin. If don't tolerate ASA due to GI issues, take Plavix instead.

Plavix works differently. Take Aspirin with food or a proton pump inhibitor (PPI) such as Nexium, Prilosec. I prefer to give a PPI + ASA.

Can I take a full ASA (325mg) instead of a baby ASA (81mg US, 100mg AU)?

No, there is a risk of bleeding with a higher dose. (200mg ASA = 3 fold bleeding risk). What about if I'm allergic to Aspirin? Can I take Plavix instead? No data (on this).

In ET, we are concerned about the CVA (stroke) risk. Can I take ASA + Plavix? No data published on this. This may increase the bleeding risk.

Secondary Prevention:

If a TIA leads to a diagnosis of MPN, should I take ASA + Plavix? No data in MPN pts.

If on ASA and have a TIA may take ASA + Plavix.

True Aspirin allergy is very rare. Ibuprofen + ASA: reduces the effectiveness of Aspirin.

In Pts with diabetes there is an increased platelet turnover. They may need to take Aspirin 2/day.

In obesity there is increased platelet activity due to leptins (hormones associated with fat cells and obesity). Take an enteric-coated Aspirin as it protects the stomach (from damage).

Secondary prevention:

I had a TIA on ASA and HU. Should I take Plavix?

There is no data on taking ASA 2/day or Plavix. All strategies are reasonable.

If a 47yo male, with ET on ASA 81mg/day has a TIA. Consider cytoreductive treatment HU or IFN.

If a 70yo PV patient with Phlebs, ASA and on HU has a DVT or AF (atrial fibrillation) what is the best treatment? The best treatment with AF is Warfarin or Pradaxa or Xarelto. May need to add ASA to prevent an arterial thrombosis.

HRT and oral contraceptives (OC):

34 yr old woman with ET on ASA 81mg/day asks can she take the OC and how much protection does she get from the ASA? A 52 yr old woman wants to use HRT.

Similar advice?

- PV carries a risk of thrombosis.
- OC increases the thrombotic risk.
- Look at prior history of thrombosis
- Look at family history of thrombosis.
- Thrombophilia (disorders with abnormal clotting).

Splanchnic vein thrombosis (SVT) 1/3 are associated with MPNs. Budd-Chiari syndrome (portal vein thrombosis) 50% associated with MPNs.

Recanalization rate with anticoagulants:

- 38% in Portal vein
- 54% Splenic vein
- 61% superior mesenteric vein.
- Bleeding 12.5/100 pt yrs.
- If no bleeding problems, continue anticoagulants. Increased risk of oesophageal varices.

In bud chiari syndrome: (clot in the portal vein going to the liver).

- Correct hematological parameters- phlebotomize
- Ascites -accumulation of fluid (in abdominal cavity) therefore parameters of 42-45% HCT don't apply.
- When fluid overload corrects, go back to 42-45% HCT target.
- Use local fibrinolytics (to try to break down the clot).
- Angioplasty
- Stent
- Liver transplant

43 yo man with ET. No prior history of thrombosis. Presents with a platelet count of 1.35 million, treated with ASA 81mg/day and has nosebleeds.

- Platelet aggregation study is abnormal.
- Von Willebrand activity is decreased by 25%.
- Discontinue ASA.
- Use HU or IFN. Arbitrary threshold to start HU 1.5 million platelets.

Same man develops lower right quadrant pain and needs surgery for diverticulitis.

- Apheresis to <800,000 platelets.
- Desmopressin
- Cryoprecipitate or Antihemophilic factor/Von Willebrand factor.

78 yo man with a history of coronary artery disease (CAD) and PV needs a total hip replacement. HCT 51, WBC 12,000, platelets 1.1 million. ASA 81mg/day. HU 1 on alternate days.

Pre-op recommendations

- HCT <45, Platelets <400,000

Post-op recommendation:

- Heparin for 35 days.
- Hold ASA
- HU and phlebs to HCT<45.

67yo woman with a history of CAD, MF. Develops painful splenomegaly following portal vein thrombosis. Following a splenectomy her platelets increase to 1.1 million, and she develops severe GI bleeding.

- 20% risk of thrombosis post splenectomy
- Mortality is 20% from thrombosis (2/30 or bleeding (1/3)

Options

- Red cell transfusion

- Platelet apheresis
- Desmopressin (↑ thrombotic risk)
- Cryoprecipitate or antihemolytic factor/Von Willebrand complex

Joy Selak, PhD: You Don't You Sick: Living Well with an Invisible Chronic Illness
(Co-author of 'You Don't LOOK Sick! Living with an Invisible Chronic Illness', (2012), with her Rheumatologist, Dr. Steven Overman)

Joy was a stockbroker and developed several chronic diseases which resulted in her having to give up the work she loved. She said having chronic disease(s) is a journey and you go through specific stages. It seems like you are alone but there are many chronic diseases.

The Invisible Chronic Illnesses	
Some of the Invisible Illnesses are:	With Symptoms as varied as:
100 types of Arthritis	Muscle & Joint Pain
Degenerative Disk Disease	Disabling Fatigue
Interstitial Cystitis	Sleep Disturbances
Multiple Sclerosis	Short-Term Memory Loss
Lupus	Skin Irritations
Sjogren's Syndrome	Allergies & Asthma
Scleroderma	Bladder & Bowel Disorders
Crohn's Disease	Abnormal Lymph Glands
Fibromyalgia	Low-Grade Fevers
Chronic Fatigue Syndrome	Nerve and Organ Pain
Trigeminal Neuralgia	Night Sweats
AND MPN's – PV, ET and PMF	Fatigue, night sweats, itching, bone pain, abdominal discomfort, weight loss, fever

"We suffer not because we are in pain. The real suffering is that we feel we are in pain ALONE."

Rachel Naomi Remen, MD

Joy went to many doctors who were unable to diagnose her conditions. She said the first lesson of chronic illness is to find the right doctor for YOU. She had one doctor who was chronically late and didn't think her symptoms were appropriate for her disease. She decided she needed to find another doctor. You only need to find one good doctor because good doctors are in a 'good doctor' club and can refer you to other good doctors! She spent 7 years worrying she was going to die of something and wasn't going

to find out what she had. After working with this doctor said told him she felt better than she had for 7 years and asked him to write a book with her about invisible chronic illnesses.

The doctor agreed and they decided to divide the book into 3 parts: getting sick; being sick and living well. Joy wrote the book and has been to many conferences sharing her story and giving travel tips, information on how to get an affordable health care plan, grief and acceptance that the dreams you had for your life will not come true, and that you have to come up with new dreams.

You need to find a doctor who understands you and who listens. You also need to be a good patient for that doctor. Report your medical history and give an annual report to your doctor(s). Recap the year, list meds and treatment, and three questions.

One of the difficulties of living with a chronic illness is living with uncertainties.

- You don't know what the side effects of the treatment will be.
- Coping with worsening fatigue.

You need to begin to gain control. Develop an intimate relationship with your symptoms. Learn when you feel the best. If resting doesn't get rid of the fatigue you need to know how to manage it.

Fighting: We hear of fighting/losing the battle in relation to disease. Fighting doesn't work. You (need to realize) you now have a different life to build and you need to redefine yourself. There is the grief of not being who you thought you would be. There is difficulty in credibility if you don't look sick.

Joy discussed her grief in having to give up work and the awful process of applying for long-term disability. It took 3 years and she had people following her who won't believe she was not going to get better.

She opened the conversation up with her self of what she could be. She focused on all the positives she had: family support, a clean environment, excellent health care, she began volunteering and drew on the gifts she had. She found she was a much better person than she had been. She discussed the unhelpful comments from well meaning "ladies at lunch". "God doesn't give you more than you can handle" or "It is to teach you a lesson". "There must be a reason" etc.

Joy's Top Ten List for Living Well, Even While Sick

1. Take care of yourself first.
2. Never, never, never give up.
3. Learn to be honest about how you are feeling.
4. Enroll in the School of Whatever Works.
5. Make friends with fatigue.
6. Live as a child. Don't hold grudges. Ask for a hug, rest when you need to.
7. Step out of the box.
8. Search for silver linings.
9. Find a way to share your gifts.

10. Be still. Think of illness as a teacher.

When fatigue strikes, we need to tell our spouses what they can do to help. Her husband asks what he can do to help. (See Joy's patient medical information forms on <http://www.mpninfo.org> under the 2013 presentations.)

Dr Mesa: Closing remarks.

Try to distil information to help your doctor. Be a steward of your own information. Having blood counts laid out on a spreadsheet, is incredibly helpful. Prepare a medical history and give a copy to each of your doctors.

(Panel of presenters: closing questions)

Question: are there concerns with taking a PPI (Xantac) inhibiting iron absorption?

Answer: PPIs impact of acid excretion and ↓Fe absorption. Pts with MPNs are not immune to losing blood in their GI tract. MPNs cause microscopic bleeding in the GI tract, which can occur constantly.

Question: does blocking acid production in the stomach effect calcium absorption?

Answer: Calcium is absorbed in the (small intestine jejunum and) ilium. It may reduce calcium carbonate absorption, but not calcium citrate.

Question: is there an ethnic aspect to MPNs?

Answer: ↑ in Ashkenazy Jews. They may have better health care. MPNs are not the same in all ethnic groups. In China MPNs are a bit different.

Question: Is it something environmental that causes MPN?

Answer: It's hard to know until we know what causes them. There is an increased incidence in Pennsylvania, but we don't know why. There is no smoking gun! It is certainly nothing you were exposed to. The causative link between smoking and lung cancer took a long time to be believed. Steve Jobs spend \$100,000 getting full genomic studies to decide on treatment.

J.G. You don't have to have the JAK2 mutation to respond the JAK2 inhibitors. All MPNs have increase JAK activation. In the future we will use genomic testing to understand and treat the disease.

Question: In MF does the spleen take over blood cell production?

Answer: When you start JAK2 inhibitors the spleen rapidly decreases. There is probably some kind of vascular anti-inflammatory effect because we see a rapid decrease in the spleen.

(P.N). If you have diabetes you may need to take 2 ASA/day due to increased platelet turnover. (Using) ASA in PV, Level 1 evidence (from the) ECLAP study. (This study) randomized 100mg ASA/day. Results 60% ↓ in risk of death and blood clots. If you take ASA less than 1/day, you loose some protection and ↑ the risk of thrombosis. Remember you have an underlying disorder that predisposes you to blood clots.

Connection between MPNs and inflammation: MF is characterised by a lot of inflammation and ↑ inflammatory cytokines. Also other symptoms: of bone pain, cachexia, fatigue, etc. JAK2 inhibitors reduce the pro-inflammatory cytokines, which contribute to the mortality of the disease.

Question: What do you do if there is a history of several different cancers in one family?

Answer: There are cancer syndromes. P53 Ca genes. The N.I.H has a clinic, which studies these families.

Question: Is there a link between donating blood and developing an MPN?

Answer: None observed. We would have uncovered it if there were one (a link).

Question: What is the effect of stress on long term progression?

Answer: We think it is negative.

A positive spirit can't overcome the illness but certainly helps.

If you have less stress you may do as well as you could have done if you hadn't had the disease.

Joy: increased stress can increase symptoms. You need to identify stress. There is also a lot of stress on physicians. We need to present ourselves as calmly as we can.

There are a lot of drugs in the pipeline. The researchers are working passionately and collaboratively with other countries.

Question: is there anything we do that can increase PV progression?

Answer: No data available on this.

You need to take Aspirin to minimize complications.



