CLINICAL VIGNETTE

Evolution of Myeloproliferative Neoplasms (MPNs)

Alexander C. Black, MD

A 52-year-old male was referred to Hematology with a several year history of slowly rising platelets. He underwent PBMC testing for bcr-abl, to screen for CML, and JAK 2, to screen for a myeloproliferative neoplasm (MPN). He was bcr-abl negative and JAK 2 + and his bone marrow aspirate and biopsy (BM ASP/ BX) showed a hypercellular (75%) bone marrow with increased numbers and clustered and hyperlobulated megakaryocytes. Cytogenetics demonstrated 46 XY with del (20) q(13.1) in 2 of 20 metaphases. In follow up he developed more polycythemia with mild thrombocytosis and was treated with hydroxyurea and aspirin 81 mg daily, given previously for coronary artery disease (CAD), and intermittent phlebotomy. In his later 50s he developed a left calf deep venous thrombosis (DVT) after a reported insect bite with infection and held aspirin and took apixaban 5 mg twice daily for 3 months and then resumed aspirin.

He missed several appointments and, one year later, returned with a 20 lb unintentional weight loss and progressive fatigue. He had new palpable splenomegaly 12 cm below the costal margin and new anemia with a hemoglobin (Hb) 9.6 gm/ dL as opposed to the 14 gm/ dL range on his 500 mg twice daily of Hydrea in prior evaluations. He underwent a comprehensive blood test evaluation which surprisingly showed a low serum folate (4.4 ng/ mL with the lower limit of normal of 8.1 ng/ mL). CT scans of chest, abdomen and pelvis just showed marked splenomegaly and repeat BM BX showed a hypercellular marrow with extensive abnormal megakaryocytes, often in sheets, and dysplastic erythroid progenitors. Flow cytometry detected 4 % abnormal myeloblasts and cytogenetics now revealed 20 of 20 metaphases with del q (20) with fluorescence in situ hybridization (FISH) confirming del 20 but no additional abnormalities. His molecular testing revealed 90% JAK 2 mutated and 3% IDH-2 mutated bone marrow cells. In addition, peripheral blood smear revealed a left shifted myeloid series with 2-4 % blasts and marked teardrops. With folic acid 1 mg daily his follow up folate was normal (14.2 ng/mL) and his Hb had increased to 11.3 gm/ dL. Given his persistent fatigue and splenomegaly, he was started on ruxolitinib 20 mg twice daily with good tolerance to date. Since ruxolitinib is a substrate of CYP3A4, he was told to check with the pharmacist on any potential new medication interactions with future prescriptions.

Discussion

Pluripotent hematopoietic stem cells (HSCs) can self-renew or begin a stepwise differentiation pathway into myeloid or lymphoid HSC. Myeloproliferative neoplasms (MPNs) and myelodysplastic syndrome (MDS) arise as a clonal disorder in a myeloid hematopoietic stem cell (HSC). MPN are characterized by bone marrow (BM) hypercellularity and expansion of one or more terminally differentiated myeloid cells, red blood cells (RBCs), neutrophils or platelets. MDS is characterized by dysplastic abnormal hematopoietic progenitor cell maturation and peripheral blood cytopenias. Both conditions have a variably increased risk of transformation into acute myeloid leukemia (AML).[1] Excluding chronic myeloid leukemia (CML), the 3 main MPNs in declining prevalence are polycythemia rubra vera (PRV), essential thrombocytosis (ET) and myelofibrosis (MF) with the primary elevation being RBC, platelets and WBC respectively. In MF, as opposed to PRV and ET, the dominant hematological issue is not excess cell production but progressive loss of BM hematopoiesis due to BM fibrosis with resulting cytopenia and splenomegaly due to extra-medullary hematopoiesis. MDS subtypes are characterized by the degree of cytopenia, the percentage of abnormal myeloblasts and cytogenetic and molecular abnormalities.

Both conditions can evolve over time with MPNs shifting to another subtype and MDS changing from low to higher risk. PRV patients have a risk of transforming into MDS, AML or MF of 10% at 10 years and 25 % at 25 years.[2] In another nested control cohort study of over 11,000 patients, there was a 3-5 fold increase in hematologic malignancies, including in patients never exposed to hydroxyurea.[2] Our patient presented with classic PRV with a clinical course lasting 9 years before evolving into MF and MDS. His 1st bone marrow had 10 % of metaphases with del 20 and his transformation bone marrow had 100 % del 20 metaphases, demonstrating progression of the sub-clone associated with his MF and MDS.

The vast majority of MPNs have one of several identified mutations in a few genes related to cytokine receptor signaling in which a cytokine like erythropoietin (EPO) binds to the cell surface EPO receptor which generates an intracellular signal through the Janus Activated Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway. Another pathway involves the platelet production stimulating cytokine thrombopoietin (TPO) which binds to the cell surface TPO receptor, MPL. Calreticulin (CAL-R) encodes a calcium binding protein located in the endoplasmic reticulum which interacts with MPL to induce intracellular signaling. In PRV well over 95% of patients have either the classical JAK exon 14 V617F mutation or one of several exon 12 mutations.[3] In ET approximately 60 % of patients have a mutation in JAK 2 and 20-25 % in CAL-R and 5 % in MPL and 10-15 % no known

molecular marker.[4] In MF, 60 % have JAK 2 mutations, 20-25 % CAL-R mutations, 7 % MPL mutations and the rest no known mutation. These molecular changes led to development of several oral JAK 2 inhibitors, the first and most commonly used being ruxolitinib.[3]

The vast majority of patients with MPN survive to years, often many years. With PRV and ET, patients who do not transform generally live for decades. Therapy for PRV and ET involves suppression of Hb or platelets respectively into a target range shown to decrease the risk of stroke in both and congestive heart failure in PRV.[5] The PRV Hb target is 14 gm/ dL using hydroxyurea, an antimetabolite, and/ or phlebotomy. The ET platelet target is 300-600 using hydroxyurea or anagrelide, a phosphodiesterase 3 enzyme inhibitor which reduces platelet production by megakaryocytes.[1] Both PRV and ET confer an increased risk of venous and arterial thromboembolic events, which are more effectively prevented by aspirin than warfarin,[6] so aspirin 81 mg daily is used except in patients under 60 without atherosclerotic disease risk factors.

The prognosis of MF is significantly worse than with PRV or ET. Clinical factors associated with a poorer prognosis include age > 65 years, WBC > 25 x 10-3/ uL, Hb < 10 gm/ dL, peripheral blast % > 1 and the presence of constitutional symptoms.[5] Cytogenetic and molecular changes have also been correlated with poorer prognosis particularly complex cyto-genetic changes and mutations in specific genes. This patient had > 1% peripheral blast and constitutional symptoms. He also had cytogenetic and FISH abnormalities and small percent IDH-1 mutation, which based on prognostic algorithms would give an anticipated survival of 6-7 years.[5] Ruloxitinib was approved for treatment of MF based on documented im-provement in constitutional symptoms,[3] with dosing based on platelet count. Given a normal platelet count CC started on full dose oral ruxolitinib 20 mg twice daily with mild cytopenia and fatigue but overall excellent tolerance to date.

MDS also has a widely accepted prognostic algorithm, the International Prognostic Scoring System – Revised (IPSS-R). CC was low risk based on the lack of significant cytopenia, specifically a Hb > 10 gm/ dL and platelets > 100 x 10-3/ uL and neutrophils > 0.8 x 10-3/ uL, and good prognosis cytogenetics, with isolated del 20, and bone marrow blast %, 2-5 with a survival estimated at 5.3 years.[7] He did not need demethylating agent therapy with either azacytidine or decitabine, which had been shown in higher risk MDS to delay onset of leukemia and to prolong survival. If his EPO < 500, he would be a candidate when his Hb < 10 gm/ dl to receive erythropoiesis stimulating agent (ESA) treatment with either recombinant erythropoietin or darbepoietin. The applicability of MF and MDS prognostic algorithms when both conditions are present, however, has not been established.

In the future if he develops worsening cytopenia or increasing peripheral blasts he could be a potential candidate for an allogeneic stem cell transplant (SCT), the only potentially curative treatment for MF.

REFERENCES

1. **Tefferi A**. Chronic myeloid disorders: Classification and treatment overview. *Semin Hematol*. 2001 Jan;38(1 Suppl 2):1-4. Review. PubMed PMID: 11242595.
2. **Frederiksen H, Farkas DK, Christiansen CF, Hasselbalch HC, Sørensen HT**. Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study. *Blood*. 2011 Dec 15;118(25):6515-20. doi: 10.1182/blood-2011-04-348755. Epub 2011 Oct 28. PubMed PMID: 22039256.
3. **Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, McQuitty M, Hunter DS, Levy R, Knoops L, Cervantes F, Vannucchi AM, Barbui T, Barosi G**. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012 Mar 1;366(9):787-98. doi: 10.1056/NEJMoa 1110556. PubMed PMID: 22375970.
4. **Grinfeld J, Nangalia J, Baxter EJ, Wedge DC, Angelopoulos N, Cantrill R, Godfrey AL, Papaemmanuil E, Gundem G, MacLean C, Cook J, O'Neil L, O'Meara S, Teague JW, Butler AP, Massie CE, Williams N, Nice FL, Andersen CL, Hasselbalch HC, Guglielmelli P, McMullin MF, Vannucchi AM, Harrison CN, Gerstung M, Green AR, Campbell PJ**. Classification and Personalized Prognosis in Myeloproliferative Neoplasms. *N Engl J Med*. 2018 Oct 11;379(15):1416-1430. doi:10.1056/NEJMoa1716614. PubMed PMID: 30304655.
5. **Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, Van Dyke D, Hanson C, Wu W, Pardanani A, Cervantes F, Passamonti F, Tefferi A**. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011 Feb 1;29(4):392-7. doi:10.1200/JCO.2010.32.2446. Epub 2010 Dec 13. PubMed PMID: 21149668.
6. **Barbui T, Finazzi G, Falanga A**. Myeloproliferative neoplasms and thrombosis. *Blood*. 2013 Sep 26;122(13):2176-84. doi: 10.1182/blood-2013-03-460154. Epub 2013 Jul 3. Review. PubMed PMID: 23823316.
7. **Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, Bennett JM, Bowen D, Fenaux P, Dreyfus F, Kantarjian H, Kuendgen A, Levis A, Malcovati L, Cazzola M, Cermak J, Fonatsch C, Le Beau MM, Slovak ML, Krieger O, Luebbert M, Maciejewski J, Magalhaes SM, Miyazaki Y, Pfeilstöcker M, Sekeres M, Sperr WR, Stauder R, Tauro S, Valent P, Vallespi T, van de Loosdrecht AA, Germing U, Haase D**. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012 Sep 20;120(12):2454-65. Epub 2012 Jun 27. PubMed PMID: 22740453; PubMed Central PMCID: PMC 4425443.

Submitted March 15, 2019