

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Recent Advances in Classic *BCR-ABL*-negative Myeloproliferative Disorders

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H&O What are the myeloproliferative disorders and what have been their historical methods of treatment?

AT Myeloproliferative disorders (MPDs) comprise one of three major categories of myeloid neoplasms; acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are the other two. The MPDs are operationally subclassified into “classic” and “nonclassic” variants. The former include those originally considered by Dr. William Dameshek in 1951: polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myeloid leukemia (CML). The “nonclassic” MPDs include chronic neutrophilic leukemia, chronic eosinophilic leukemia, hypereosinophilic syndrome, systemic mastocytosis, chronic myelomonocytic leukemia, and others. It should be noted that some of the nonclassic MPDs display histologic features shared by MDS. My focus for the current discussion is the *BCR-ABL*-negative classic MPDs: PV, ET, and PMF.

In PV, the cornerstone of treatment has been phlebotomy. Low-dose aspirin therapy was recently shown to have additional antithrombotic value. Although not tested in a controlled setting against placebo, cytoreductive treatment with hydroxyurea is believed to further reduce thrombosis risk in high-risk patients with PV. In contrast, a randomized study has demonstrated the antithrombotic effect of hydroxyurea in high-risk ET. Low-risk patients with ET are managed by a “watch-and-wait”

strategy. Current therapy for PMF is suboptimal; palliative treatment modalities include drugs (eg, erythropoietin, androgen preparations, corticosteroids, thalidomide [Thalomid, Celgene], lenalidomide [Revlimid, Celgene]), splenectomy, and involved-field irradiation of the spleen or other sites of extramedullary hematopoiesis. Treatment with either myeloablative or reduced-intensity conditioning allogeneic stem cell transplantation (ASCT) is used for selected patients with high-risk disease.

H&O How is classic *BCR-ABL*-negative MPD diagnosed?

AT Historically, the diagnosis of PV, ET, and PMF required fulfillment of a list of “consensus” criteria. In PV, red cell mass (RCM) measurement was used by some but not other investigators as part of the diagnostic work-up. The recent description of *JAK2* mutations (V617F and exon 12 mutations) in virtually all patients with PV has further undermined the diagnostic use of RCM measurement, which is now considered obsolete and abandoned by many centers including my own. Therefore, modern diagnosis in PV starts with peripheral blood analysis of *JAK2* mutations and erythropoietin level followed by bone marrow examination as indicated. Bone marrow examination remains essential for accurate diagnosis in both ET and PMF.

H&O What assays are used in each form of classic *BCR-ABL*-negative MPD?

AT In PV, diagnostic work-up starts with serum erythropoietin level measurement and peripheral blood mutation

screening for *JAK2V617F*, which is detected in approximately 95% of PV patients. If the mutation status is positive and the serum erythropoietin is low, the results are interpreted as being highly suggestive for PV. In such an instance, bone marrow examination is encouraged but not essential to confirm the diagnosis. A negative peripheral blood screening for *JAK2V617F* makes PV diagnosis unlikely but not impossible; in the February 1, 2007, issue of the *New England Journal of Medicine*, novel *JAK2* exon 12 mutations were reported in *JAK2V617F*-negative PV cases with low serum erythropoietin level. Therefore, if the index of suspicion is high, both bone marrow examination and mutation screening for exon 12 *JAK2* mutations are recommended to clarify the diagnosis in a *JAK2V617F*-negative case. It should be noted, however, that the presence of *JAK2V617F* does not distinguish PV from other MPDs as the mutation is present in approximately 50% of patients with either ET or PMF.

In ET, one has to be certain first that a high platelet count is not the result of a reaction to insult, such as infection, surgery, iron deficiency, or other conditions associated with reactive thrombocytosis. Once the possibility of reactive thrombocytosis is considered unlikely, it is reasonable to screen for *JAK2V617F*; a positive test practically excludes reactive thrombocytosis from the differential diagnosis but it is neither essential nor specific for the diagnosis of ET. Therefore, an examination of the bone marrow is ultimately required for making the specific diagnosis of ET. Expertise in bone marrow histologic evaluation of MPDs is needed to make reliable diagnosis of both ET and PMF and avoid misdiagnosis of cellular-phase PMF, as ET or MDS with fibrosis as PMF. More importantly, because of therapeutic implications, one should screen for *BCR-ABL* during the diagnostic work up of both ET and PMF; CML can occasionally mimic both ET and PMF in its presentation.

H&O What research led to the development of molecular targeted therapy, and what is the status of such therapy, in this setting?

AT There is currently major interest by industry for the development of small-molecule targeted therapy in MPDs; the key incentive in this regard is the recent discovery of a close association between these diseases and an activating *JAK2* mutation (*JAK2V617F*). This discovery was brought about by four independent investigative groups, one from the United States and three from Europe, and it confirmed what had been long suspected: JAK-STAT signaling is the central pathogenetic pathway in PV and related disorders. The primary focus has been on *JAK2* inhibitor therapy. In this regard, several compounds have shown preclinical activity against cell lines, animal mod-

els, and primary cells from affected patients. Accordingly, the first wave of clinical trials involving such compounds is anticipated to begin in the second quarter of 2007.

H&O What is the role of molecular monitoring of treatment response and assessment of minimal residual disease in this setting?

AT The short answer is that it remains to be studied. However, quantitative assessment of *JAK2V617F* allele burden carries the potential for use in molecular monitoring of treatment response and assessment of minimal residual disease. Some investigators have already used such an approach to follow PMF patients after ASCT and PV patients following treatment with interferon alpha. The question remains, however, whether *JAK2V617F*-associated "molecular" response in PMF or PV predicts overall outcome and therefore can facilitate selection of superior therapy. What should be the threshold below which the natural history of the disease is expected to be favorably affected? Wishful thinking in this regard is not helpful for patients and such questions should be addressed in prospective controlled studies.

H&O What treatment strategies are used when a chronic myeloproliferative condition becomes acute?

AT If a chronic myeloproliferative condition becomes acute, it is a major problem for the patient. There is little precedence of success in this setting. Nevertheless, patients with leukemic transformation are often offered induction chemotherapy that is usually used for de novo AML. ASCT can then be considered if the patient's condition either reverses back to the chronic phase of the disease or goes into remission. Alternatively, patients can be referred for participation in experimental treatment trials.

H&O How prevalent is this transformation?

AT ET carries the least risk, among the classic *BCR-ABL*-negative MPDs, of blastic transformation; 10- and 20-year incidence rates are approximately 2% and 7%, respectively. The corresponding incidence rate estimates for PV and PMF are 5% and 20% and 10% and 30%, respectively. The presence of *JAK2V617F* has not been shown to affect either survival or blastic transformation in ET or PMF.

H&O What is the role of stem cell transplantation in MPD?

AT There is no doubt regarding the value of ASCT in select, high-risk, patients with PMF. The particular treat-

ment modality has no role in the treatment of either ET or PV in the absence of disease transformation into myelofibrosis. Furthermore, even in PMF, the risk of ASCT, in terms of regimen-associated mortality and morbidity, is not justified for all patients. At my institution, we utilize the Mayo Prognostic Scoring System (Mayo PSS) for PMF in order to select the right group of patients for the most appropriate therapy, including ASCT. The Mayo PSS is based on four adverse prognostic variables: hemoglobin below 10 g/dL, platelet count below $100 \times 10^9/L$, leukocyte count either below $4 \times 10^9/L$ or above $30 \times 10^9/L$, and monocyte count at least $1 \times 10^9/L$. In the absence of any adverse feature (low-risk disease), median survival is expected to exceed 10 years and such patients are usually observed without any treatment. The presence of two or more adverse features (low-risk disease) predicts a median survival of less than 5 years and ASCT is a reasonable therapeutic option in this instance. In general, I recommend participation in experimental drug therapy for patients with only one adverse prognostic factor (intermediate-risk disease). I am even more comfortable with such a treatment strategy in the presence of solitary 13q- or 20q- cytogenetic abnormality, which is associated with good prognosis. Finally, the presence of *JAK2V617F* in PMF does not appear to affect transplant outcome.

H&O Can you discuss the assessment of quality of life for patients with MPD?

AT A large, international quality-of-life (QOL) study was published in the January 1, 2007, issue of *Cancer*, which reported on 1,179 patients with MPDs. The study found fatigue as a major QOL issue in patients with all three disorders. Other complications affecting QOL included pruritus, night sweats, bone pain, fever, and weight loss. Not surprisingly, the incidence and sever-

ity of these constitutional symptoms was the highest in patients with PMF. Interestingly, however, fatigue was self-reported as a major complaint in 85% of PV patients and 72% of those with ET. Another major situation that affects QOL in PMF is the need for frequent red blood cell transfusions. Therefore, treatment that alleviates anemia in PMF has major benefit for patients even if it does not improve survival.

H&O Where do you see research headed in the future in this setting?

AT It is necessary to determine not only the pathogenetic but also the therapeutic relevance of *JAK2* mutations in MPDs. We need to know, as soon as possible, whether targeting these mutations with small-molecule drugs will make a difference for our patients. Furthermore, it is becoming increasingly evident that *JAK2V617F* is not the only important mutation in these diseases and the others need to be discovered as well. Translation of laboratory discovery into clinical practice requires partnership between patients, physicians, clinical pathologists, and laboratory scientists. Examples of commendable efforts in this regard include the chronic MPD Education Foundation cofounded by Joyce and Bob Niblack and the Chicago-based MPD Foundation led by its president Robert B. Rosen.

Suggested Readings

Tefferi A, Gilliland DG. JAK2 in Myeloproliferative disorders is not just another kinase. *Cell Cycle*. 2005;4:1053-1056.

Tefferi A, Pardanani A. Mutation screening for JAK2V617F: when to order the test and how to interpret the results. *Leuk Res*. 2006;30:739-744.

Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international internet-based survey of 1179 MPD patients. *Cancer*. 2007;109:68-76.