

Is Bloodletting Facing Extinction?

By Ruben Mesa, MD

I had just explained to my patient with low-risk polycythemia vera (PV) that her therapy will consist of phlebotomy and a “baby” aspirin when she turned to me and said, “Bloodletting... you mean, like they used for George Washington? And an aspirin? Is that the best modern medicine has for my disease?” Perhaps soon, therapy for the myeloproliferative disorders (MPDs) will move beyond these archaic and non-specific interventions. The seminal discovery of the JAK2^{V617F} mutation, and its role in MPD pathophysiology, has led to an explosion of investigation into these diseases, highlighted on Saturday in Dr. Radek Skoda’s Ham-Wasserman Lecture and in the MPD Education Session.

Today, in four separate MPD Simultaneous Sessions, the clinical and therapeutic implications of JAK2^{V617F} will be explored. Particularly exciting is this afternoon’s session on Myeloproliferative Syndromes, from 1:30 to 3:00 p.m., in which the first results of specific JAK2 inhibitor trials will be discussed by Dr. Srdan Verstovsek of M. D. Anderson Cancer Center, who has played a pivotal role along with Dr. Ayalew Tefferi of the Mayo Clinic and others in initiating these trials. Current JAK2-inhibitor trials in MPDs have focused first on myelofibrosis — both primary disease and that which has evolved from PV or essential thrombocythemia. In a phase I/II study of INCB018424, an oral JAK2 inhibitor, preliminary results demonstrated a rapid reduction in splenomegaly and significant improvement in constitutional symptoms. Dr. Verstovsek said, “The very early clinical results with INCB018424 have surpassed our expectations. We are very excited about the prospects of providing the patients, for the first time, with potentially effective therapy specifically targeting the abnormality found in their disease.”

Additionally, preliminary results of two ongoing trials of JAK2 inhibitors, XL019 and CEP701, will be presented. “Interestingly, current trials include patients regardless of their JAK2 mutation status, based on *in vitro* data suggesting JAK2 wild-type patients may still respond to these inhibitors,” said Dr. Animesh Pardanani of the Mayo Clinic, whose laboratory investigates these agents.

“The pipeline of potential JAK2 inhibitors is strong, and the current agents being tested are promising for MPD therapy,” said Dr. Tefferi. Indeed, many other JAK2 inhibitors that are in pre-clinical development will be discussed today, such as TG101348, AZ60, ITF2357, and AZ-0. “If the JAK2 inhibitors prove safe and efficacious in myelofibrosis, testing could soon proceed to earlier disease such as ET and PV,” Dr. Verstovsek said.

Decades passed between the discovery of the Philadelphia chromosome and the development of a targeted therapy for chronic myeloid leukemia, imatinib. Comparatively, the explosive pace of JAK2-targeted therapy is unprecedented, with only two years between the initial identification of the JAK2^{V617F} mutation in MPDs in early 2005 and the multiple clinical trials of JAK2 inhibitors that are accruing patients in 2007. “We all hope the efficacy of the JAK2 inhibitors approaches the optimism and promise both MPD patients and physicians feel,” concluded Dr. Tefferi. Perhaps one day soon we will finally be able to retire bloodletting.