

ADVANCES IN LLM

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

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JAK2 Inhibitors in Polycythemia Vera

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H&O What is polycythemia vera (P vera), and how is it currently treated?

AQC P vera is one of the myeloproliferative neoplasms, which is a term that encompasses a series of myeloid disorders that share several features. The 3 most important myeloproliferative neoplasms are P vera, essential thrombocythemia (ET), and primary myelofibrosis. P vera is characterized by an increase in hematocrit and red blood cell mass. It is often accompanied by an increase in the white blood cell count and the platelet count. Historically, patients with P vera have been managed with phlebotomies in order to decrease the hematocrit to within the normal range. If phlebotomies are not sufficient to achieve this goal, patients are then usually treated with hydroxyurea, an oral form of chemotherapy. Hydroxyurea helps to control not only the red cell count but also the white count and the platelet count because it essentially suppresses the bone marrow function. Phlebotomies are not needed in many patients receiving hydroxyurea.

H&O How has the recent discovery of a recurrent point mutation in the Janus kinase 2 (JAK2) gene (JAK2 V617F) challenged prior treatments of P vera?

AQC The JAK2 V617F mutation, which was discovered in 2005, brought about 2 big changes in the field of myeloproliferative neoplasms. First, it changed the way

we classify and diagnose these patients. For instance, patients with P vera nowadays can be diagnosed very easily with a simple blood test. In patients with a JAK2 mutation and low erythropoietin plasma levels, the diagnosis can be readily made without a bone marrow biopsy. That is important, because 98% of patients with P vera will carry this mutation. For those in whom no JAK2 V617F mutation is found, it has been shown that other mutations in the same gene, but in different places (not at the 617 residue), can be found. Additionally, almost all of those patients will have low erythropoietin levels. The combination of those 2 factors is what makes the diagnosis in a huge number of patients. The manner in which a diagnosis is now made has been simplified enormously with the discovery of the mutation.

The second big change involves potential treatment approaches. The discovery of the JAK2 V617F mutation unveiled a new target to treat in these patients. JAK2 is an enzyme that is mutated in these patients so that it is constitutively active; it signals continuously and promotes the growth of myeloid cells in the bone marrow. It has kinase activity, and there are many agents that are inhibitors of kinases. After the discovery, many companies embarked on the mission of discovering JAK2 inhibitors, and there are multiple agents in clinical studies undergoing preclinical characterization for the treatment of patients with the JAK2 mutation. Several of them are quite far along in clinical development. Most of these agents have been tested in myelofibrosis, but a few have been

tested in patients with P vera or ET. Examples include CEP-701 (Lestaurtinib, Cephalon) and INCB018424, now known as ruxolitinib (Incyte). Phase II data from clinical studies with these JAK2 inhibitors have been presented. Most patients with P vera included in these studies were refractory or poor responders to the standard of care. The CEP-701 study included 39 patients, combining both P vera and ET. It showed activity, as some patients had a decrease in the size of their spleens, many improved symptomatically, and some actually had decreased phlebotomy requirements. In many cases, those responses were not considered complete in accordance with the European LeukemiaNet response criteria, which require normalization of both the platelet count and the white blood cell count, as well as the hematocrit; disappearance of splenomegaly; and disappearance of all symptoms related to the disease. Even though many patients showed some degree of improvement, not many patients achieved complete remission. Similarly, when ruxolitinib was tested in the same type of patients (those with ET and P vera, most of whom were resistant or refractory to hydroxyurea), many experienced some improvement, either in symptoms, spleen size, white counts, or platelets. However, in aggregate, a complete response was achieved by approximately 25% of patients with ET and approximately 50% of patients with P vera. These responses need to be put into context, because most of these patients had shown signs of resistance or refractoriness to standard of care therapy. Even though responses are certainly encouraging, they may be actually better in patients who are newly diagnosed.

An important question is whether or not patients with P vera or ET need to be treated with JAK2 inhibitors. It is a relevant consideration because the lifespan of patients with P vera or ET is really long. The life expectancy of patients with ET is basically the same as that of age-matched controls, and the life expectancy of patients with P vera is only slightly shorter than age-matched controls. It is then clear that JAK2 inhibitors will not prolong survival and their role may instead be in the prevention of disease-associated morbidity. Treatment objectives in patients with P vera and ET relate mostly to the prevention of complications, and the main complication in this population is the development of thrombosis and hemorrhage. Clotting is a major problem that is linked to the elevation in the white blood cell count more so than the elevation in the platelet count. It is unknown whether JAK2 inhibitors prevent thrombotic complications because the follow-up in the studies is too short. In the CEP-701 study, however, 5 patients developed such complications while receiving the JAK2 inhibitor. One could argue that it is possible to achieve response with

these agents, but not prevent the main problem, which is the development of thrombotic complications, and, perhaps, the progression to acute myeloid leukemia. Only a longer follow-up may solve that question.

H&O How might therapy with ATP-competitive JAK2 inhibitors affect P vera patients' symptoms and overall quality of life?

AQC One of the main characteristics of these JAK2 inhibitors is that they improve symptoms remarkably, and that is shown more strikingly in patients with myelofibrosis. Patients with myelofibrosis are riddled with constitutional symptoms, such as fatigue, night sweats, weakness, cachexia, weight loss, and loss of appetite. In those patients, the use of JAK2 inhibitors leads to significant improvement in all of those symptoms. In contrast to patients with myelofibrosis, patients with P vera or ET tend to be asymptomatic. When symptoms are present, they are generally mild. Pruritus is one of the most common symptoms in these patients. An ongoing phase II study in ET and P vera is showing that JAK2 inhibitors can improve symptoms quite remarkably. The relevancy of symptom improvement, however, is much stronger in patients with myelofibrosis compared to patients with P vera or ET.

H&O How does treatment with JAK2 inhibitors in P vera patients differ from other treatment methods?

AQC JAK2 inhibitors are oral medications, so they are very easy to administer. Hydroxyurea is also an oral medication that is generally well tolerated, although it may have long-term complications, such as skin ulcers, which have not yet been seen with JAK2 inhibitors. A historical concern exists that hydroxyurea may have the potential to induce acute leukemia in patients treated for long periods (typically decades) of time. This outcome has not been observed with JAK2 inhibitors, but again, the follow-up is very short, and the long-term toxicity profile of these agents remains to be seen.

Another option for P vera patients is phlebotomies. Phlebotomies for P vera are, of course, a cumbersome and bothersome treatment because they need to be done in a hospital/clinic setting and repeated multiple times, making them less convenient than taking a pill.

The other option for P vera and ET is the use of pegylated interferon alfa, which has been around for several decades. Based on pioneering work done by Dr. Richard T. Silver in the field of myeloproliferative neoplasms and Dr. Moshe Talpaz's work in chronic myelogenous

leukemia, it has been shown that the drug has activity in P vera and ET. Pegylated interferon alfa-2a (Pegasys, Hoffmann-La Roche) has a completely different toxicity profile than that of JAK2 inhibitors, and includes fatigue, flu-like symptoms, myalgias, and low-grade fevers. These pegylated forms of interferon can be self-administered via subcutaneous injection once per week, and they are much better tolerated than standard interferon. Jean-Jacques Kiladjian's group in France, as well as our group at M.D. Anderson Center, have shown that these agents—particularly pegylated interferon alfa-2a—are extremely active in P vera and ET. They induce hematologic response rates in 80–90% of cases and molecular responses in approximately 50% of cases, some of which are complete responses. Pegylated interferon alfa-2a is the only agent so far that has been able to eradicate the JAK2 mutation in P vera or ET. The importance of those molecular responses remains unclear, as the long-term consequences of eliminating a mutation are unknown, and whether those patients will have an advantage in terms of survival or prevention of thrombotic complications or progression to acute myeloid leukemia with available follow-up has yet to be determined. None of the JAK2 inhibitors tested thus far have been able to eliminate the mutation, and in fact, they have minimal effect on the JAK2 mutant allele burden. While the activity of pegylated interferon alfa-2a seen in 2 ongoing phase II studies is very exciting, its activity versus hydroxyurea (standard of care) needs to be tested.

H&O What are some of the purported targeted agents with notable *in vitro* JAK2 inhibitory activity and varying degrees of JAK2 specificity that are currently undergoing clinical evaluation?

AQC JAK kinases, or JAK proteins, are a family of 4 different proteins: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK2 inhibitors have different inhibitory activities against the family. For instance, ruxolitinib is very potent against JAK1 and JAK2, but not a very effective JAK3 or TYK2 inhibitor. The same is true for other inhibitors. In general, they all have a certain degree of activity against all JAK kinases but they are selective against a subset of them. Thus, how much they inhibit each kinase differs from compound to compound. Some of them are JAK1 and JAK2 inhibitors, and some of them have a degree of JAK3 inhibitory activity as well. There are other agents that are more specific against JAK2. BMS-911543 (Bristol-Myers Squibb) is a JAK2 inhibitor that is extremely specific for JAK2 and inhibits the protein almost exclusively. A study with this compound has just opened at M.D. Anderson Cancer Center.

The other issue is the kind of inhibitory activities these agents have against other kinases outside the JAK2 family. The CEP-701 compound has activity against FLT3, and that appears to account for the gastrointestinal toxicity seen with this agent. Several other agents also have activity against FLT3. Therefore, it is not only the differences in terms of how well they inhibit the JAK family of proteins, but also the differences in terms of how many other kinases these agents inhibit outside the JAK family of kinases. The combination of both spectra of inhibitory activities renders different toxicity profiles.

H&O Can you discuss the effects of the selective oral JAK1/JAK2 inhibitor ruxolitinib?

AQC As I mentioned, ruxolitinib is a potent JAK1 and JAK2 inhibitor; the activity against JAK1 and JAK2 is much higher compared to the activity against JAK3 and TYK2. Therefore, this is an example of an agent that selectively inhibits JAK1 and JAK2. That is unlike CEP-701, for instance, which is a very active JAK2 inhibitor as well but also inhibits other kinases, such as FLT3. Whether that is important or not for the clinical activity of the drug is debatable, but, as previously mentioned, inhibition of other kinases may produce different toxicity profiles. Perhaps the most important difference between the toxicity profiles of various JAK2 inhibitors is the presence of gastrointestinal toxicity, such as nausea, vomiting, and diarrhea. The latter appear to be found predominantly in the JAK2 inhibitors that also have some activity against FLT3. Ruxolitinib, on the other hand, has little to no activity against FLT3, so gastrointestinal toxicity is neither the most worrisome nor the most common side effect of this compound. Because this compound is so potent against JAK1 and JAK2, and because JAK2 is so important for hematopoiesis, the main side effect of ruxolitinib is cytopenias, particularly thrombocytopenia.

H&O How will the use of JAK2 inhibitors play a role in the future direction of P vera treatment?

AQC This is a difficult question to answer at this point. Certainly, a longer follow-up with these agents is warranted, as current follow-up is still very limited. The most critical voices in the field of myeloproliferative neoplasms will question the need for these agents in P vera or ET, which are disorders not accountable as major sources of mortality. They may be hesitant to the notion of subjecting these patients to lifelong JAK2 inhibitor activity, especially when long-term data regarding the toxicity have not been established. These are valid arguments, because what will happen with these agents in the long-term remains

unknown. So far, they appear to be extremely safe, which is the main counterpoint to those who are currently skeptical about the use of these agents in P vera or ET. Alternatively, one may question the need to use JAK2 inhibitors when hydroxyurea is available. Again, this is a very valid point that mandates the activity and safety of JAK2 inhibitors to be tested in a randomized fashion, ideally in a phase III trial, against that of hydroxyurea in the frontline setting, especially since most of the data currently available for P vera and ET treatment with JAK2 inhibitors are based on patients who have already failed hydroxyurea.

We have several agents with significant activity: hydroxyurea, pegylated interferon alfa, and JAK2 inhibitors.

However, until we have comparative studies with these agents, it will be difficult to prove that one is more effective over the others. Luckily, these studies are ongoing.

Suggested Readings

ClinicalTrials.gov. Study of the JAK inhibitor ruxolitinib administered orally to patients with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). <http://clinicaltrials.gov/ct2/show/NCT01317875?term=ruxolitinib&rank=1>. Identifier NCT01317875.

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