

# ADVANCES IN LLM

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

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## JAK2 Inhibitors and Myeloproliferative Neoplasms

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**H&O** What is the pathogenesis of myeloproliferative neoplasms (MPNs) in regards to JAK2?

**SV** MPNs are Philadelphia (Ph) chromosome-negative diseases of the bone marrow and blood, traditionally divided into 2 groups: Essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) are the so-called classic MPNs, while others that are less common are called atypical MPNs and include hypereosinophilic syndrome, chronic eosinophilic leukemia, and systemic mastocytosis.

About 4 years ago in classic Ph chromosome-negative MPNs—ET, PV, and PMF—a mutation in a gene called JAK2 was discovered. The JAK2 protein, a tyrosine kinase associated with receptors for many growth factors and cytokines, is important for the growth and function of cells in the normal, healthy state. When a cytokine or a growth factor binds to a receptor on the cell surface, the JAK2 tyrosine kinase associated with the receptor gets phosphorylated. This event initiates downstream signaling through other multiple proteins (eg, STATs), leading to the growth of the cell, among other things. However, in a disease state, the JAK2 tyrosine kinase is mutated and autophosphorylated, which basically means that the enzyme is active all the time. The role for the mutated JAK2 in the pathophysiology of MPNs has been proven with elegant mouse studies, where the expression of mutated JAK2 gene in mouse bone marrow cells led to the development of PV and subsequently to myelofibrosis.

It is interesting that the same JAK2 mutation has been found in 3 different diseases—ET, PV and PMF—that have different presentations and outcomes. ET patients have a near-normal life expectancy; PV patients have a life expectancy of approximately 20 years; PMF

patients have a markedly reduced life expectancy of only 5–7 years on average. That tells us right away that there must be other factors contributing to the clinical presentation or phenotype of the patient. The JAK2 mutation is unlikely the initiating factor that leads to the disease, but rather a significant contributing factor.

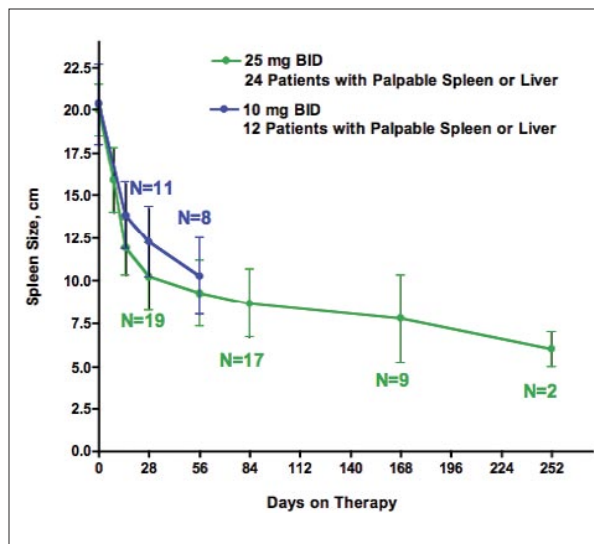
On the positive side, however, this is the first time that we have found something that is relatively specific for this group of diseases. About half of the patients with ET and half of the patients with PMF have a JAK2 mutation—the V617F JAK2 mutation. Importantly, about 95% of PV patients have that mutation.

Other rare mutations in the JAK gene have been described in patients with PV, as have mutations in a receptor for thrombopoietin (called MPL) in patients with PMF. These are the 2 additional significant mutations that have been recognized. There are sporadic cases of other mutations within the JAK2 gene that also lead to the autophosphorylation of the JAK2 and the activation of JAK-STAT pathway, which is why we believe that the inhibition of JAK2 tyrosine kinase will positively affect the disease and benefit many patients. That is the hypothesis behind the development of the JAK2 inhibitors.

**H&O** What JAK2 inhibitors are currently being studied?

**SV** *INCB18424*: This medication, made by a company called Incyte, is currently in a phase II study for patients with PMF or MF post-ET or post-PV. The initial part of the study was conducted from June to November of 2007 with an accrual of 32 patients. The starting dose of 25 mg BID was rapidly identified as the maximum tolerated dose; the dose-limiting toxicity was thrombocytopenia.

The main benefit of this therapy so far has been a very significant reduction of enlarged spleen, which is one of the hallmarks of PMF (Figure 1). Enlargement of the spleen, and sometimes also the liver, happens in these patients due to the so-called “extramedullary hematopoiesis”. Because of a worsening fibrosis, the bone marrow in PMF patients is unable to produce blood cells; therefore, other organs, primarily the spleen or liver, take on that role. If one surgically removed an affected enlarged spleen from a PMF patient, one would find bone marrow cells within it. Over time, approximately 80% of patients develop significant splenomegaly.



**Figure 1.** INCB18424 effective in reducing spleen size.

With the development of a very big spleen, patients have difficulties with malnutrition and body wasting (eg, diarrhea, constipation) due to, in part, mechanical compression of their stomach. Significant circulatory problems including portal hypertension with gastrointestinal bleeding and pulmonary hypertension associated with heart and lung failure may develop. Liver failure is also an important development in many patients.

The INCB18424 is effective as it can lead to a massive reduction of the big organs (eg, splenomegaly) with significant improvement in the quality of life (QOL) of these patients. Current efforts are to further document all clinical benefits of this therapy, with the hope that in the next year, a registration study will be allowed to commence, primarily for patients with very enlarged spleen and poor QOL.

What is interesting with this medication is that the result of therapy is equal in patients with the JAK2 V617F mutation and in those without it. There is no difference in their outcome, which is difficult to explain at this point. The medication affects JAK2 as well as JAK1 tyrosine kinase. Since JAK1 is involved in cytokine signaling, this may, in part, explain the beneficial effect of the therapy in all cases. What is evident is that the biology of the disease has markedly changed in patients who are on therapy, not just by clinical results but also by the measurement of numerous cytokines—proinflammatory and proangiogenic cytokines that are known to be highly expressed in patients with myelofibrosis, all return to normal within a month. Therefore, the benefits of this therapy are speculated to range between having cytostatic activity due to the inhibition of JAK2 and anti-inflammatory activity that results from inhibiting the malignant clone.

Although the disease is not eliminated (the percentage of cells with the mutation in samples obtained from patients on therapy decreases), disease control is much better in these patients. Patients continue to live with the disease, which is now markedly better controlled with a massive reduction in organomegaly and disease-related symptoms, and they may enjoy life to its full extent again. Patients gain weight, their performance status improves, and their activity level is much higher.

In terms of side effects, significant lowering of platelets happens in approximately 30% of the patients on the highest (25 mg twice a day) regimen. The dose level in the study has been modified to avoid any myelosuppression, and different dose schedules are being investigated before the final determination of design for a possible regulatory approval study next year.

**XL019:** XL019 is from a company called Exelixis, which started a phase I study in July of 2007 in patients with PMF. The results with this medication have shown so far, like with INCB18424, a significant reduction in spleen size and improvement in QOL. What is different is that XL019 does not cause any myelosuppression. However, the initial investigation in a limited number of patients revealed mild central and peripheral neurological system toxicity. The study was redesigned in the earlier part of this year, and new dosing and schedules are currently being investigated to identify those that would provide benefit without any toxicity. Study results will be presented at American Society of Hematology (ASH) annual meeting in December of 2008.

**TG-101348:** Developed by TargeGen, TG-101348 is in a phase I study that started in early 2008 in patients with PMF. We are currently awaiting clinical results, which will be presented for the first time also at the ASH annual meeting.

**SB1518:** SB1518 is from a company called S\*Bio Pte Ltd. located in Singapore, and it is a JAK2 inhibitor as well as a Flt3 inhibitor. Flt3 is a molecule that is expressed on myeloid cells, and when abnormal, it is known to be an adverse prognostic factor in patients with acute myelogenous leukemia (AML). A phase I study of SB1518 is currently underway for patients with myeloid hematologic malignancies, and the initial results are expected to be presented at the ASCO meeting next year.

**Lestaurtinib (CEP701):** This drug, developed by Cephalon, is also a JAK2 and Flt3 inhibitor. In fact, it has been developed as an Flt3 inhibitor for therapy of AML patients. When the JAK2 mutation was discovered, CEP701 was found to be as effective a JAK2 inhibitor as an Flt3 inhibitor. A phase II study of CEP701 was done in 22 patients during the fall of 2007, showing response in 6 patients. Responses were primarily reductions in spleen size, but there were also significant improvements in blood cell count. The dosing schedule was the same as

that used for AML. A phase I study has now been initiated to find out whether one would be able to provide a higher dose and possibly achieve better overall results in PMF patients.

**H&O** How important is it in the development of new drugs that they are selective to the mutation?

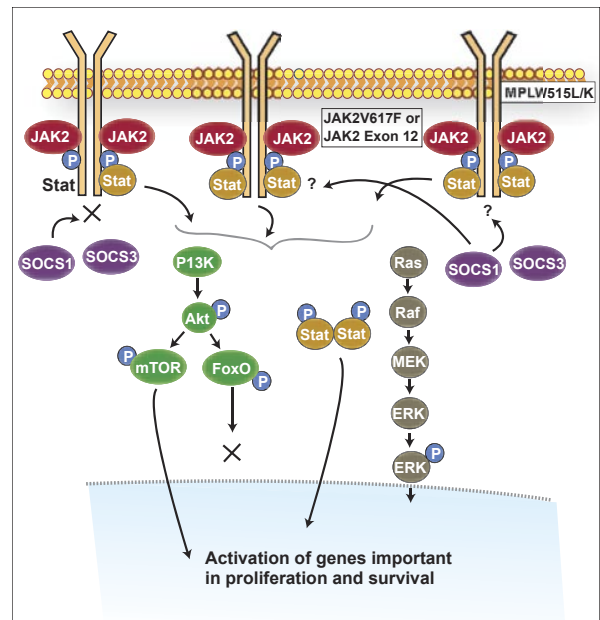
**SV** This is a very interesting question. One would expect that most activity, if not all, would be in patients with a mutation because malignant cells depend on continuous high expression of the mutated JAK2, and that activity would not be seen in patients without the mutation. However, the outcome of therapy with INCB, as described above, has been a surprise as it is effective in patients with both mutated and wild type JAK2. It can be speculated that the inhibition of JAK1 plays a role, but in order to explain the biology of this, tissues from patients on therapy—particularly from spleens that shrink significantly—need to be obtained. This is, of course, not possible.

None of the medications being investigated in the clinic are selective for the malignant clone with JAK2 mutation. They are all ATP binding site inhibitors, meaning that they prevent the energy source to bind to the JAK2 enzyme. However, we know that the JAK2 mutation is in the pseudokinase domain, which results in a conformational change of the kinase part of the enzyme. This conformational change leads to the activation of the enzyme and is not tied to the ATP binding to it. Therefore, the inhibition of the ATP binding with currently available JAK2 inhibitors equally affects wild type and mutated JAK2 enzymes. However, one may perhaps expect that there would be preferential inhibition of the cells with the JAK2 mutation because they depend more on the continuous activity of the mutated JAK2.

Perhaps the second generation of JAK2 inhibitors will be selective for the mutated JAK2 protein and be able to eliminate the malignant clone in patients with the mutation. For now, however, I think that it is good news that current JAK2 inhibitors, INCB18424 in particular, are proving effective in patients with or without the mutation, seeing that only half of PMF patients have a JAK2 mutation.

**H&O** Could patients develop resistance to JAK2 inhibitors as they did with BCR-ABL inhibitors?

**SV** Yes, this is a possibility over time and a good parallel is the development of resistance to imatinib mesylate, a BCR-ABL inhibitor, in chronic myelogenous leukemia (CML) patients. In both cases, the medications are tyrosine kinase inhibitors by virtue of being ATP binding site inhibitors. Therefore, it is possible that with prolonged therapy we will witness the development of resistance to JAK2 inhibi-



**Figure 2.** Various ways of interfering with mutated JAK2 protein are being investigated.

Data adapted from Levine RL, et al. *Nat Rev Cancer*. 2007;7:673-683.

tors, which is likely due to the development of mutations in the ATP binding site. We do not have any evidence that this has happened so far in any of the patients on therapy. We will then likely discover differences between various JAK2 inhibitors, their potency against different mutations, and their usefulness in various clinical situations, similar to the current state of affairs in CML.

**H&O** Are there any studies investigating whether alternative alleles can account for MPN?

**SV** Many laboratories around the world are working to identify new genetic or epigenetic abnormalities in MPNs, as it is pretty clear that the JAK2 mutation is not the disease-initiating abnormality. These efforts may also help identify abnormalities responsible for the disease in patients without JAK2 mutation, which make up half of MF patients, for example. There must be some commonalities among JAK2 mutation-positive and -negative cases, as they present with an identical clinical picture. Unlike CML, which is unique because all the cases are driven by the BCR-ABL oncogene, MPNs are a group of neoplasms with similar clinical presentation that likely are a result of abnormalities related to a common intracellular pathway (eg, growth factor receptor-JAK-STAT pathway).

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**H&O** Are there inhibiting factors that affect the protein stability of the JAK2 mutation, possibly to weaken the mutation but not wild type JAK2?

**SV** A new way of research is investigating alternative ways of interfering the mutated JAK2 protein, in order to develop therapies that would truly be selective for the malignant clone. At this time, this type of research is in its preliminary stages and limited to the preclinical testing of different hypotheses using cell lines and patient samples. For example, the role of SOCS family of proteins is being investigated, as they may have a role in increasing mutation stability (Figure 2). The other aspect of preclinical research worth mentioning is the possible development of medications that would bind specifically to the mutated JAK2 protein, as mentioned earlier.

**H&O** How far are we from seeing JAK2 inhibitors as first line-therapy?

**SV** Of the different MPNs, the most aggressive and most deadly disease is PMF, either primary or secondary to ET or PV. There are no effective therapies for this disease and the life expectancy is about 5–7 years. At this point, we are limited in our efforts to help these patients because current medications have no potential to alter the natural course of the disease; there is only supportive, palliative care. No medication has been approved, therefore, as a therapy for PMF. Bone marrow transplant is the only therapy with curative potential, but it carries a high mortality rate; low intensity transplant is being investigated as an alternative.

Because of such a somber situation, the development of any new therapy that would provide clinical benefit to PMF patients would be a major achievement. This is clearly a medical area of unmet need. Therefore, emerging data on the efficacy of JAK2 inhibitors—INCB18424 in particular—as seen in marked reduction in enlarged spleens and profound change in patients' QOL, provides hope that these medications will at least successfully control the disease and make the patients live a good life. Recent evidence that good control of bone marrow disease without disease elimination prolongs patients life (azacitidine [Vidaza, Celgene] therapy for myelodysplastic syndrome patients) gives hope that similar results can be seen with JAK2 inhibitor therapy in PMF. I hope that within 3 years, we will have the first JAK2 inhibitor approved as therapy for PMF.