JAK2 Negative? Understanding Gene Mutations and Treatment for MPNs

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Brady Stein, MD
Assistant Professor, Department of Medicine, Hematology Oncology Division
Feinberg School of Medicine, Northwestern Medicine

Audience Member:

For the myelofibrosis patients who are JAK2 negative, are there any developments for us?

Dr. Stein:

So absolutely. At the very beginning, we talked a lot about JAK2, but we also talked about half the patients with essential thrombocythemia, and half the patients with myelofibrosis lack a JAK2 mutation. So there was a diagnostic gap. There must be something explaining why we see some of those features.

There must something behind this, because in many ways you couldn't tell by looking at the blood counts or the patient if they had a JAK2 mutation or if they lacked it. So the clinical picture can be for many patients very, very similar. So why do patients look similar in certain ways but lack the JAK2 mutation?

So in 2013, so in December there were two reports, the first two reports of the gene many of you know about called calreticulin or CALR. So this is the gene mutation that essentially fills the diagnostic gap. So if you lack JAK2, and you have ET or myelofibrosis, there is a very, very high likelihood that you have calreticulin gene mutation. This is something that actually can now, I think Quest [diagnostics] is now testing for it and it's now, there are definitely commercial assays.

And we are working on our internal validations that we can test for it. So that's perhaps the biggest breakthrough in terms of diagnosis. What is the mutation that explains some of the, the blood and bone marrow perhaps and clinical findings? If we look at the therapies, what's very, very interesting and we learn a lot from the clinical trial about the disease. That's sort of reverse, you want to know everything you can know about the disease and then do the clinical trial.

But in this era, with the pace so rapid, developments quick, we learn some things about the disease from the clinical trials, and it turns out that patients on JAK inhibitors seemed to respond equally well whether they have a JAK2 mutation or whether they lack a JAK mutation. And that doesn't make so much sense. It's not very intuitive to even most of the hematologists that we talk about.

Well, it turns out that this calreticulin gene mutation seems to, if we talk about this switch of this pathway, it looks like this calreticulin in a different way activates the pathway. So there are reports of patients with known calreticulin mutation who respond to JAK inhibitors. So there may be specific therapies designed for those with calreticulin gene mutation, but some of the therapies we already use may work just as well, because some of the features of the disease are similar.

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