Discovery of the Calreticulin Mutation: What Does It Mean for Patients?

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Dr. Verstovsek:
To go a little bit back in time and talk about something that appears to be important for diagnostic purposes, if not for targeting, this is the recent discovery of a calreticulin mutation because the major news is, American Society of Hematology meeting six months ago, and since then, two publications in major medical journals, New England Journal of Medicine, described this in much more detail.

And many patients come forward asking about the brute therapeutic potential of this discovery, but the, more so, I think it's important for us to understand who should be tested and what is the purpose of the testing right now in everyday practice?

Dr. Levine:
It's a great question and I think that, fundamentally, what we know, based on the data that's come from now, many different labs all over the world, is that the calreticulin mutation is totally exclusive, meaning it occurs in patients that are always JAK2 wild-type, and it occurs in patients that either have ET or myelofibrosis.

And what I think is really helpful is that there are 50 percent of patients with both diseases that are negative for JAK2 and most of those patients—not all of them, but most—have calreticulin mutations. And what that means is that for patients who don't know what the genetic basis of their disease is, who don't have a positive marker to follow, who don't have any tests that come back positive other than their blood counts, this gives an answer.

And I think that is important for diagnosis, and I think the new World Health Organization criteria that will come out next year will require this as a major criteria. And what that means is you're going to have to test all your patients. The biggest question is, do you test everybody for all the genes at once, or do you test only the JAK2 negative patients, calreticulin?

A lot of that's going to depend on where you are, do you run a gene panel, do you run single gene tests, access to test reimbursement? My hope, and at least what I hope will happen, is that we'll send gene panels in our patients. Because it's

quite cumbersome to test a patient for JAK2 and then come back in two weeks and say, now we're going to test you for calreticulin, even if, in this sort of perfect world, that's a reasonable sort of on-the-blackboard approach.

I think our patients want us to run the tests right when they come in—and give us the answer. They don't want to spend three months having a workup. They want an answer when they get their bone marrow read, and I think that's where we're going. Does it have other biologic questions? Absolutely, and may have actually cool immunologic questions, but it's just the early phase.

Dr. Odenike:
I would agree, I mean, at our institution, you know, we are running gene panels now as are many academic institutions. These mutations can also co-occur with others, some of the ones that we have, you know, alluded to, so it makes sense to just take one sample and screen for all these different mutations and then be able to give the patient a readout.

What will be most exciting, which you know, we all believe will be coming, at some point, in the not so distant future, are drugs that somehow target, you know, the mechanism of action, of these mutations and can therefore hopefully bring meaningful benefit to our patients.

Dr. Verstovsek:
So, to summarize, it looks like a JAK2 V617F mutation and calreticulin mutations are exclusive of each other in EP and PV.

There is a third one called MPL mutation or MPL, that is present in a few percentages, and that is the ballpark, or the treatment that drives the disease growth if you like, right, the target active JAK-STAT pathway that is common to all the patients.

In all the other mutations that we mentioned with difficult names may or may not be present and one patient may have three mutations or five mutations or seven mutations. It's hard to know unless you do all this testing for the future if not imminently applicable.

Dr. Levine:
I think you're right, Srdan. I think the way to think about it, and what I tell patients, is that everyone has something that activates the JAK pathway, whether it's JAK2 or calreticulin or MPL or something we're not smart enough to know. The other mutations are the fine-tune. They help us determine if someone's going to have a very aggressive course that they're going to have an indolent course.

Are they going to respond to some of these other, more atypical agents or not? And so, those are sort of ways to fine tune the disease, but they don't define the disease, whereas the JAK2, MPL, calreticulin, I think really define these diseases, also because they're really not seeing, in any significant extent, in other immunologic diseases at any high frequency, whereas all the other mutations we've talked about are seen, essentially, in all leukemias.

And so, there are sort of the MPN-specific or you know, top-tier mutations, the ones that our patients really need to follow, and have a test for it no matter where they are. They should know their JAK2, MPL, and calreticulin status. But the other mutations, I think it depends on how they're doing, if they're doing well and they have indolent disease, maybe they don't need to be tested.

But if their disease is acting up, I think they should have a much broader genetic test to make sure that there's not something that they don't understand without that data, and I think that's the approach of our team.

Dr. Verstovsek:
And it seems to me that for the everyday use, one-time testing appears to be enough for now. At the time of that first visit in the institution where there is a panel of 28, 30 genes—and not to really do it on the therapy. The patient is on the ruxolitinib (Jakafi) or investigational therapies as a routine, perhaps in investigational therapy as something to follow as a, quite a few studies, to see whether there is some genetic testing.

Dr. Verstovsek:
But in every practice, treating patients with lenalidomide or Hydrea, or Jakafi, looks like there is no real need to monitor patients' response to therapy by repeating either the bone marrow or the genetic testing.

Dr. Levine:
Also, there's two sort of aspects of that we need to be cautious about. The first is that JAK2 and MPL and calreticulin, as far as I've seen, are very stable. If they're there at one point in the disease, they're always going to be there. And if they're not

there, they're not going to show up in here, if somebody already has the disease… I'm not aware of patients ever who have PV and are negative for those and then they come a year later with the same disease.

However, some of these other mutations can pop up during a course. The best examples, a really nice study up at the Mayo Clinic of IDH mutations, that when they occur, patients can have a high risk of developing leukemia in the next 18 months.

The question, which I think you're asking, which is, we don't know, how often do you test, you know, which ones to test for?

So our approach, at least, is we only test when a patient's disease seems like it's changing—their counts change, they don't feel right, their response to a drug stops. And then, whenever we do a bone marrow, we set aside the genetics. We'd like to get some of these other mutations, and I think that that's, you know, fundamentally how we do it. Would we like to get to a point where maybe, we could use this as a surveillance approach? Absolutely.

But that's going to take years and lots of studies to really show, because it's going to take a lot of patience to figure out what to do with that information.

Dr. Verstovsek:
So maybe use it in occasional situations where there is a significant progression, a change, certainly when there is a transformation to occupy the leukemia question, but not really to use it in every practice, to say hey, how is the, your genetic problem today?

Dr. Levine:
Absolutely, dramatic reduction in the drug you need, resistance to a drug, you see, you know, cells in the bone marrow, but in the blood that you never saw before. I think that's exactly right.

Dr. Odenike:
Yeah, I would agree. I think that the idea of serially monitoring these mutations probably would only come into play when we have drugs that target these mutations besides the only one we see, you know, whether decline or the effect of these, of the drugs on the mutations may be.

But with the currently available therapy, in most cases, that would not be necessary. And if we have a specific drug targeting a specific mutation, it is likely that those kinds of serial surveillance would already be built into the clinical trial. By routine practice, this would be done for diagnostic purposes, and then, if the disease should progress.