Current and Future Treatments for Polycythemia Vera (PV)

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Andrew Schorr:
Dr. Heaney, let's talk about where we had been traditionally with treatments. I know there have been some changes within the last year. We're going to cover that in a little greater depth to understand how things have changed. So if you go back a couple of years—or even further—where were we with treatment?

Dr. Heaney:
Back when I was a fellow, the treatments included things like radioactive phosphorus and some fairly strong chemotherapy drugs like busulfan (Busulfex) and pipobroman (Vercyte), which was used in Europe. I think through some of the research that was done in the '70s and into the '80s, we learned that those drugs can be associated with a higher risk of leukemia in patients who used those. So those treatments have largely been banned. So now the mainstay of treatment is phlebotomy—so taking blood from someone as if they were a blood donor but usually discarding that blood. And also other medicines like hydroxyurea (Hydrea), which can also help to control the platelet count and the white blood cell count, and aspirin to help reduce the risk of clots.

Andrew Schorr:
What about the use of interferon at all? Has that come into play?

Dr. Heaney:
Interferon is a drug and I think folks at MD Anderson, among others, have really played a role in bringing interferon into the MPNs in general, and a number of centers in the U.S. and Europe have shown that interferon can be a highly active treatment. And, in fact, some patients who take interferon can have complete remissions in the marrow and not have any evidence of p. vera [polycythemia vera], even using very sensitive molecular tests. Now, the downside to interferon, though, is that it's a medicine that can be difficult to take. Patients who take interferon can have flu-like symptoms and their quality of life can sometimes be worse than if they weren't taking it.

And so you get to this situation where you have to balance the risks and the benefits of interferon.

Andrew Schorr:
Dr. Verstovsek, so many people with PV, they have phlebotomy. Others have hydroxyurea, too. So help us understand where that comes in and does it work for most people?

Dr. Verstovsek:
So the goal of therapy initially would be to control the blood cell count. With that, the symptoms would, in many patients, improve. So phlebotomy is the nice way to decrease the red blood cell count, and the goal is to decrease the red blood cell clot by measuring hematocrit, which was mentioned, below 45 percent. Hematocrit is basically the volume of red blood cells in the blood. So 45 percent or lower is the goal because it has been shown that high levels are associated with a high risk of thrombosis.

So everybody with polycythemia vera deserves the phlebotomy as needed to control the hematocrit, and we give baby aspirin to make blood flow easier to decrease the thickness of the cells, particularly platelets in this condition. Now, looking back then, we were able to dissect patients that would be at higher risk of blood clotting than the others. So traditionally, we have two factors that are important for decision-making. Either patient has a high risk of blood clotting or a low risk of blood clotting within the group of PV patients.

And usually the age over 60, or having a history of blood clots are the two factors that say yes, you are at a high risk, or you are not. If you are at a high risk—let's say you are older than 60 or you have a history of blood clots, then we would add to phlebotomy and aspirin a medication that would reduce the blood cell count and control it better or eliminate the need for phlebotomy and maintain the red blood cell count low all the time.

The first choice usually is hydroxyurea, but interferon has a role in it. And by guidelines, in fact the two are equally available as a first-line defense in which country we are talking about; there are many factors that influence that, not just the accessibility but also tolerance and desire of the patients and the age of the patients, for example. And between the two, we can actually control the disease very well. Hydroxyurea is a pill. You take it daily. It can control the counts in many patients to satisfaction. I usually tell my patients it's like controlling the blood pressure; you take the pill, the blood count is low.

You keep taking it for the rest of your life. With interferon, it's injectable. It is standardly given three times a week as injectable, but new forms of interferon are now available which are injectable weekly or even every two weeks. In Europe, there is a new preparation being tested in PV studies, which is an injectable every two weeks—which means a better tolerance, less frequent injections, better tolerance because it comes with the flu-type symptoms.

So interferon is coming to age and the attractive part is what was mentioned; possibility of improving the bone marrow, improving the biological features of the disease, and perhaps even eliminating the cells with the mutation that spreads in the normal cell body. We talk about the JAK2 mutation. These cells may go away in about 20 percent of the patients after a year-and-a-half on interferon. So there are advantages of interferon in terms of efficacy, but perhaps the tolerance is still the issue.

Andrew Schorr:
Okay. So, Dr. Heaney, so over the last several months, then, we had approval of a drug for an expanded indication, a drug we already had in myelofibrosis; ruxolitinib, or Jakafi. Some people say Jakafi and we think of—Jakavi in Europe it's called, and in other countries. At any rate, so this was expanded.

What was the idea behind that? Where does that fit in?

Dr. Heaney:
There are some patients—and it's a small number, but there are some patients who aren't able to tolerate hydroxyurea. Hydroxyurea, although many patients do very well with the drug for years and years, does have some side effects. Some patients have ankle ulcers that are attributable to the hydroxyurea and will never get rid of those ulcers as long as they're taking hydroxyurea. And there are some patients who just don't have adequate control of the symptoms of polycythemia, the blood counts with hydroxyurea. So for those individuals, ruxolitnib is an alternative.

And in the clinical testing that led to the approval in polycythemia vera, ruxolitnib actually did a very good job of controlling many of the symptoms that are associated with polycythemia vera, often controlling the blood counts by itself. And also, as Dr. Verstovsek mentioned, reducing the allele burden, which means that it's also getting to the heart of the actual cells that are causing the polycythemia. It's a drug that is probably not something that most patients need to take, at least at this point with the available clinical data. But it's a drug for patients whose disease really can't be controlled with hydroxyurea.

Andrew Schorr:
Dr. Verstovsek, both of you are involved in research, so you're looking ahead. And looking back, you've been involved with these trials for a long time. So any other comment you want to make about adding a JAK inhibitor as available for some patients, where that comes in? Would you echo what Dr. Heaney says?

Dr. Verstovsek:
This is very interesting development. We learned a lot about biology of myeloproliferative neoplasms, and we know that in each patient, whether this is polycythemia vera patient or essential thromobocythemia or myelofibrosis, the two other MPNs; everybody has a hyperactivity of what we call the signaling pathway, a cascade of proteins inside the bone marrow cells. We call this JAK-STAT pathway. The JAK is the first of these proteins, the stat is second, and then they activate all the others. And there are these pathways hyperactive in the bone marrow cells in patients for many different reasons.

And most of the time because of a mutation in a JAK2 enzyme, which is called JAK 2V617F, and the JAK inhibitors inhibit this JAK stat pathway. That's why they work. They decrease the growth of the cells. They decrease the inflammation that comes with this disease. We know that symptoms also are related to the inflammatory state that comes with the disease. So the JAK inhibitors would decrease the number of the cells that are growing without control, decrease the symptoms, and that's why they are useful. And it was pointed out very well that they are useful and approved in United States for patients who do not do well on Hydrea**.**

Not too many patients are like this; perhaps 10 percent of the patients are refractory to the hydroxyurea, and there's about 10 percent perhaps intolerant to it. It's a smaller fraction. But for these patients, we didn't have too many options and now we do. What I'd also like to emphasize is how the scope of our benefits—or analysis of benefit—has changed over time.

At the beginning, we were always focused much on red blood cells.

We know that the platelet number is not the risk factor for thrombosis. Now we have a number of studies suggesting that the white cell count is important, perhaps. And some suggest that we need to take account into that. But when we look at the benefit, we look at the normalization of the red blood cells, white cells, platelets, symptoms and the spleen. So this is what we want to achieve. We want to control all of this together.