**Transcript Details**
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www.reachmd.com
info@reachmd.com
(866) 423-7849

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Understanding the Underlying Mechanisms in Myelofibrosis

**Announcer:**
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by GSK. Here's your host, Dr. Charles Turck.

**Dr. Turck:**
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and here to help us better understand the underlying mechanisms of myelofibrosis is Dr. Serge Verstovsek, who's a Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. Dr. Verstovsek, welcome to the program.

**Dr. Verstovsek:**
My pleasure. Thank you very much for having me here.

**Dr. Turck:**
So let's just dive right in, Dr. Verstovsek. What role does the JAK-STAT pathway have in myelofibrosis?

**Dr. Verstovsek:**
The hyperactivity of the JAK-STAT intracellular signaling pathway is the key pathophysiological abnormality in all patients with myelofibrosis. We know that the JAK-STAT pathway, the intracellular signaling pathway, is a cascade of proteins that makes cells do different things, and the JAK-STAT pathway is involved in blood making. It's also involved in the immunological system – activational immune system – and in some other activities in the bone marrow and other tissues in patients or in a regular person. But what happens in myelofibrosis is because of different genetic abnormalities, we have hyperactivity of the JAK-STAT pathway; my patients call it a highway. It's always open, always running, and makes cells grow. Inflammation is another part where the JAK-STAT pathway has a role, and so when you have a hyperactivity of JAK-STAT pathway in myelofibrosis patients, what do you get? You get uncontrolled cell growth and uncontrolled inflammation, which then clinically are relevant for that person.

**Dr. Turck:**
And are there any other genetic alterations that may contribute to the pathophysiology of myelofibrosis?

**Dr. Verstovsek:**
Understanding why the hyperactivity of JAK-STAT pathway happens is the key for understanding the biology of myelofibrosis in the first place.

There are three usually mutually exclusive mutations in three different genes that happen in myelofibrosis patients, and the most common and widely known one is the mutation of the JAK-2 gene, JAK2 V617F mutation, which is expressed in about 50 percent of the patients. Calreticulin mutation is present in about 30 percent of patients, and in about 10 percent we have mutation in the MPL or "maple" gene.

**Dr. Turck:**
Now as I understand it, anemia is quite common among patients with myelofibrosis. So would you tell us how that develops?

**Dr. Verstovsek:**
You are right. We would say that there is a paradox here. You have a myeloproliferative neoplasm – that's what myelofibrosis is, MPN. You have a high productivity of JAK-STAT pathway that makes cells grow and makes people not feel well because of uncontrolled inflammation. And then you have anemia; how can this be if the cells grow without control?

Well the one consequence of uncontrolled cell growth – and sometimes we do find patients with early-stage myelofibrosis where they

have too many white cells or too many platelets in the blood – the uncontrolled growth of these malignant cells in the bone marrow leads to a reaction of the bone marrow environment in a way that fibrosis develops, scar tissue in bone marrow. That's where the name comes from – myelofibrosis. Myeloid stands for the bone marrow cells; fibrosis is a scar tissue in the bone marrow. And that fibrosis leads to the contradictory clinical scenario that you ask about. Instead of having too many cells, people develop anemia.

**Dr. Turck:**
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Serge Verstovsek about the pathophysiology of myelofibrosis.

So Dr. Verstovsek, what are some of the key biomarkers in myelofibrosis that we need to be aware of?

**Dr. Verstovsek:**
As part of the diagnostic process, we would test for presence of these mutations that activate the JAK-STAT pathway: JAK2 mutation, calreticulin, or MPL mutations. That will cover about 90 percent of patients, and they're mutually exclusive as I mentioned, and the presence of any of these in addition to clinical findings – fibrosis description in the bone marrow and other findings from the blood and physical exam – would lead one to make a diagnosis of myelofibrosis.

But then there are other key biomarkers that we test for. There might be in about 40 percent of patients at the time of diagnosis abnormalities in different chromosomes that carry genes. And we also are aware of genetic complexity beyond these driver mutations that activate the JAK-STAT pathway. They affect the outcome of the patients. Having mutations in other genes like EZH2, SX1, and IDH have been shown by many to have prognostic information, and they affect the outcome of patients and lead us to a different therapeutic approach.

For example, presence of multiple other mutations, and everybody in academic centers would go by testing through NGS for the presence of other mutations other than the driver mutations, and the identification of multiple genetic abnormalities, which we call genetic complexity, would lead us to advise the patients to go to the bone marrow transplant sooner rather than later. Genetic complexity translates very commonly to more aggressive disease, higher likelihood of untimely death, and transformation to acute leukemia. That happens in about 20 to 25 percent of myelofibrosis patients.

So looking for biomarkers – molecular biomarkers, in particular, if not only for a grade of fibrosing bone marrow or abnormalities in chromosomes – are standard practice and become very informative for prognostical importance for decision making in everyday practice.

**Dr. Turck:**
And before we close, Dr. Verstovsek, what are some key highlights you'd like our audience to take away from our discussion today?

**Dr. Verstovsek:**
Understanding the underlying biological problem in any disease is a crucial one, and until 2005, we did not have a clue what is myelofibrosis all about. And then, the discovery of the JAK2 mutation and then follow-up with the calreticulin and MPL mutations, established very well that in myelofibrosis and in other myeloproliferative neoplasms, the hyperactivity of JAK-STAT pathway is the key abnormality, which eventually led us to develop inhibitors of that JAK-STAT pathway. And now we have three different JAK inhibitors out there approved for the management of patients with myelofibrosis. Understanding genetic complexity that we talked about not only for the prognostication purposes, but for developing other non-JAK-STAT pathway inhibitors as a therapeutic medication for the management of myelofibrosis patients is where the field is going.

**Dr. Turck:**
Those are all great takeaways for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Serge Verstovsek, for joining me to discuss myelofibrosis. Dr. Verstovsek, it was great having you on the program.

**Dr. Verstovsek:**
Thank you so much, it was my pleasure.

**Announcer:**
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