Stephanie Halene, MD, PhD

Nikolai Podoltsev, MD, PhD

Transforming Research For Blood Malignancies

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In June 2013, Nikolai Podoltsev, MD, PhD, Assistant Professor of Medicine (Hematology), began caring for newly-diagnosed patient Fred DeLuca, co-founder of the global SUBWAY restaurant chain. Dr. Podoltsev and other staff at Smilow Cancer Hospital cared for Mr. DeLuca as he underwent treatment for leukemia leading to remission, which allowed him to proceed with an allogeneic stem cell transplant under the care of Stuart Seropian, MD, Associate Professor of Medicine (Hematology). When his disease later recurred, Dr. Podoltsev and other Yale specialists, including Stephanie Halene, MD, PhD, Associate Professor of Medicine (Hematology), treated Mr. DeLuca until his death in September 2015.

In April 2016, Mr. DeLuca's wife, Elisabeth DeLuca, met with Dr. Podoltsev and offered to support his research into blood malignancies through a grant from The Frederick A. DeLuca Foundation. She soon expanded this offer of support to fund research by Dr. Halene, Dr. Seropian, and others at Yale Cancer Center and Smilow Cancer Hospital. These grants have already fostered research collaborations and resulted in the publication of nine manuscripts, which illuminate new findings in hematological cancers.

Now, thanks to the Foundation, research in the field of blood malignancies by Cancer Center scientists is about to multiply and accelerate. In April, a substantial gift launched the new DeLuca Center for Innovation in Hematology Research. "It's transformative for us," said Dr. Podoltsev.

Leukemias and lymphomas are the most familiar subtypes of blood cancers, but the list is long. Dr. Podoltsev's research and medical practice, for instance, address not only acute myeloid leukemia (AML) but also lesser-known blood malignancies such as myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs).

One of the papers supported by the Foundation was published in October 2018 in *Blood Advances*. Dr. Podoltsev and his co-authors from Yale School of Medicine (Hematology Section) and Yale School of Public Health performed a nationwide statistical analysis of two standard treatments for older patients with an MPN called polycythemia vera (PV). PV occurs when bone marrow makes too many red platelets, thickening the blood and slowing its flow. This can lead to clots, embolisms, heart attacks, and strokes.

One standard treatment is therapeutic phlebotomy, in which excessive blood is removed to prevent thrombosis or blood clots. Another is hydroxyurea (HU), a 150-year-old drug that suppresses the production of blood cells. The National Comprehensive Cancer Network (NCCN) recommends HU as a first-line therapy for older PV patients, but some physicians won't prescribe it because of doubts about its efficacy or misplaced fears that it can lead to acute leukemia.

Dr. Podoltsev and his co-authors used the massive SEER-Medicare database to analyze the history of 820 PV patients. Phlebotomy cut the risk of thrombosis nearly in half and reduced the risk of death by 35 percent. For patients who took HU, the data was equally striking. There was a direct correlation between the length of time a patient took HU and the decreased risks of thrombosis and death.

In short, the study strongly confirmed the guideline recommendations. That wouldn't normally be news, but the researchers also found that, despite the clear benefits of these therapies, only 64 percent of PV patients received phlebotomies and only 60 percent were prescribed HU. "We hope this convinces some physicians that they should use HU for PV patients who are at risk of developing clots," said Dr. Podoltsev. "Our study adds to the evidence that it works—we just have to use it."

A second paper, published this March in the *Journal of the National Comprehensive Cancer Network*, did a similar statistical analysis on high-risk patients with another MPN, essential thrombocythemia (ET). ET is also a blood malignancy caused by excessive production of platelets, with complications similar to those of PV. Using the SEER-Medicare database, the researchers investigated the use of HU among 1,010 patients. They found, once again, that HU was associated with a 49 percent drop in the risk of thrombosis, and a 48 percent drop in mortality. Yet a quarter of the high-risk patients didn't receive treatment with HU.

Dr. Halene also has benefitted from the support of The Frederick A. DeLuca Foundation. Among her research interests are the mechanisms that lead to MDS and acute myeloid leukemia (AML). AML and MDS are difficult to study because blood stem cells don't grow well in cultures and only few cell lines that model a patient's primary disease exist.

That's changing because of "humanized" mice designed by Richard Flavell, PhD, FRS, Sterling Professor of Immunobiology. Dr. Flavell's "MISTRG" mice have been genetically modified to have a human immune system so they won't reject grafts of human cells, including blood stem cells. The benefits for researchers such as Dr. Halene are immense.

In a paper published in *Nature Communications* in January, she and her co-authors described how they successfully engrafted human MDS cells into MISTRG mice and were able to reproduce the clonal complexity of those cells and follow the progression of the disease. "Now we can study these primary human cells," said Dr. Halene, "and see how the mutations occur and how they alter hematopoiesis"—the production of blood. "And then, importantly, we can test targeted treatments."

She is working on that with Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology. The scientists are testing PARP inhibitors in combination with other drugs against mutations of a common enzyme in MDS called isocitrate dehydrogenase (IDH). With Dr. Thomas Prebet, MD, PhD, Associate Professor of Medicine (Hematology) and Associate Director of the Myeloid Malignancies Program, they hope to bring their research to a clinical trial by this fall. New therapies for MDS are needed. Currently the only cure is a bone marrow transplant, which isn't possible for everyone.

Drs. Podoltsev and Halene are excited that the new Center will facilitate recruitment of new faculty and provide grants to young scientists eager to develop promising ideas. It will also foster collaborations between clinicians and basic scientists to test new therapies. A major focus of the Center will be a bio-specimen bank of samples taken from patients with blood malignancies.

"We will be able to annotate patient samples much better, which will lead to new hypotheses, new approaches, new ideas on what to tackle," said Dr. Halene.

It's all happening because Fred DeLuca became Dr. Podoltsev's patient in 2013. "I sent him to both Dana Farber and Memorial Sloan Kettering for opinions, and he saw very distinguished leukemia physicians," said Dr. Podoltsev, "but he always came back. I think this new Center is Mrs. DeLuca's response to the care he received here, not just by me but by Stephanie and the nurses and our transplant team and the whole staff. We're extremely appreciative of her generosity and looking forward to share the results of the research the Center will enable."

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