New findings on therapy-related myeloid cancers

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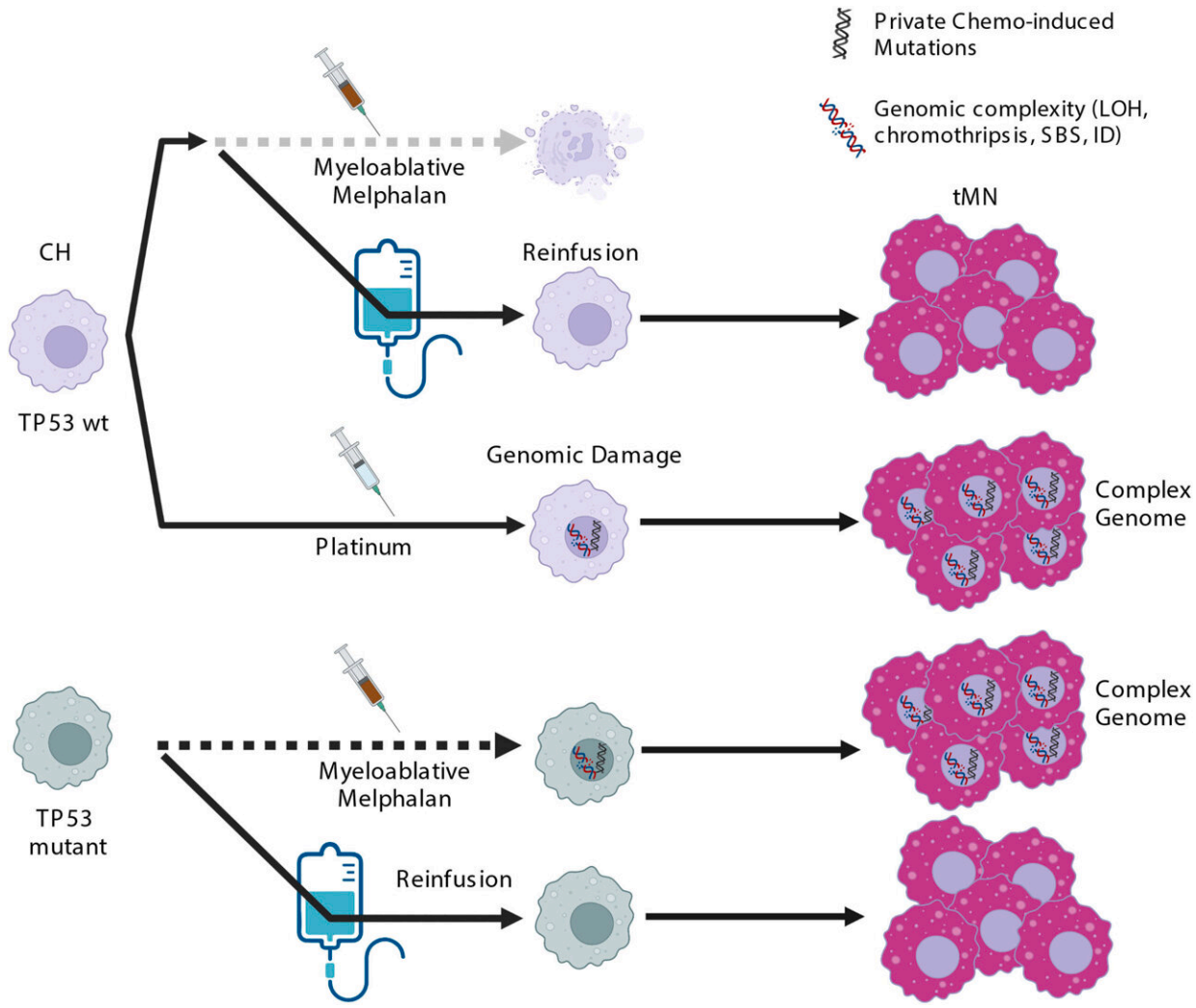

Credit: *Blood* (2022). DOI: 10.1182/blood-2022-158992

Scientists at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine have illuminated how treatments for multiple myeloma and other aggressive blood cancers can lead to future malignancies, called therapy-related myeloid neoplasms (tMNs). These findings from Sylvester's Myeloma Research Institute highlight the importance of fully understanding the long-term impact anti-cancer therapies can have on patients. The research was published in the journal *Blood*.

"By studying distinct mutational signatures associated with chemotherapy, we were able to track how pre-leukemic cells could evolve into a tMN," said Francesco Maura, M.D., co-leader of the Myeloma Genomic Lab at Sylvester, assistant professor of medicine, and co-senior author on the study. "We found that tMNs develop in different ways. They can be hypermutated or they may simply out-compete normal cells."

High-dose chemotherapy and stem cell (bone marrow) transplants can be highly effective at combatting multiple myeloma and other deadly blood cancers, but they come at a cost. These treatments can generate their own cancer-causing mutations, which years later can lead to tMNs. But until now, nobody had ever tracked the evolutionary pathway between the initial genetic variations and the cancers they can become.

Assessing genomic landscapes

In the study, first author Benjamin Diamond, M.D., and colleagues used whole genome sequencing and other techniques to assess the genomic landscapes in samples from 39 tMN patients. They found patients who had received chemotherapies with known mutagenic effects, such as melphalan or platinum-based therapies, had multiple mutations, including severe structural issues in their chromosomes, a condition called chromothripsis.

Patients who received non-mutagenic therapies showed less severe genomic variations more akin to those found in acute myeloid leukemia. In these cases, pre-leukemia cells with mutations in the TP53 gene (which protects DNA from replication errors) would still progress to tMNs, even without the extra push from mutagenic therapies.

In addition, autologous stem cell transplants, in which stem cells are extracted from the patient and reinfused after chemotherapy, did not always safeguard patients from tMNs.

"Many of the patients in the study had been treated for multiple myeloma with autologous stem cell transplants and high-dose melphalan chemotherapy," said C. Ola Landgren, M.D., Ph.D., director of the Myeloma Research Institute, co-leader of the Translational and Clinical Oncology Research Program, and co-senior author on the study.

"For these patients, we showed that tMN can develop from pre-leukemic stem cells that are removed from the body while the patient undergoes stem cell collection, and later are being re-infused as part of the autologous transplant. As a result, these cells escape melphalan chemotherapy and, once re-infused, expand because of the patient's compromised immune system."

These results show that whole genome sequencing can play a critical role in fully assessing tMN origin and evolution and could potentially guide cancer treatment. In addition, they highlight the importance of fully understanding the long-term effects of any cancer therapy.

"This study raises important questions. Before implemented in clinical practice, these results need to be validated in a larger study. Overall, our data suggest that we may need to re-think how to treat newly diagnosed patients with multiple myeloma," said Dr. Maura. "If a patient is eligible for an autologous stem cell transplant, but the patient is also at an

increased risk of tMN if given high-dose melphalan, the risk-benefit ratio may not be optimal. However, we need more data to better understand how to predict tMNs and hopefully avoid them."

More information: Bachisio Ziccheddu et al, Tracking the Evolution of Therapy-Related Myeloid Neoplasms Using Chemotherapy Signatures, *Blood* (2022). DOI: 10.1182/blood-2022-158992

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