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“Impact of Metformin on Clonal Hematopoiesis and Clinical Outcomes in Breast Cancer”

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SCIENTIFIC ABSTRACT

Clonal hematopoiesis (CH) is a common and potentially targetable, pre-malignant condition defined by the expansion of a clonal population of blood cells carrying somatic mutations in leukemia-associated genes. Cellular stressors like chemotherapy contribute to an inflammatory bone marrow niche and provide selective pressures that favor mutant clonal expansion and subsequent evolution to frank malignancy. CH in this context is characterized by chemoresistant clones, which confer a greater risk for developing therapy-related myeloid neoplasms (t-MN) which are associated with more aggressive disease. Notably, solid tumor patients have higher rates of CH that drive poor outcomes including evolution to t-MN, cardiovascular mortality, and potentially increased rates of cancer relapse. As inflammation has been implicated in the expansion of mutant clones and leukemic transformation, therapeutic approaches to target the inflammatory niche could reduce the risk of further clonal evolution. Metformin is a diabetes drug that exhibits anti-inflammatory activity independent from its anti-glycemic effects and has been studied in several cancer prevention trials. We propose using highly-sensitive error-corrected sequencing to study blood samples from a cohort of metformintreated breast cancer survivors to characterize their rates of CH after adjuvant chemotherapy. Our project will inform the use of metformin for targeting CH by comparing mutant clone size before and after 6 months of treatment and examining cancer and cardiovascular outcomes in breast cancer survivors found to have CH. Delineating these relationships will inform new screening, surveillance, and preventative strategies for CH in this vulnerable population and other malignancies where the frequency of t-MN is high.

LAY ABSTRACT

Clonal hematopoiesis describes a common pre-cancerous condition where blood stem cells gain one or more mutations in cancer-associated genes that allow them to grow and expand abnormally at the expense of their normal counterparts. Chemotherapy triggers DNA damage and inflammation within the bone marrow microenvironment prompting certain blood stem cells with adverse mutations to expand even further, significantly increasing the risk for developing very aggressive blood cancers for which current treatments are ineffective and survival is measured in months. There is a critical need for improved predictive and preventative measures for secondary blood cancers in patients who are otherwise cured from their primary cancer. Metformin is a widely-used diabetes drug that blocks several inflammatory pathways and

could have profound effects on the bone marrow microenvironment to reduce the risk of secondary blood cancers in individuals treated with particularly causative chemotherapeutic agents. We will study how treatment with metformin affects clonal hematopoiesis and disease outcomes in women who received chemotherapy after surgery for breast cancer. Exploring how inflammation after chemotherapy exposure affects mutant blood stem cells leading to predisposition for secondary blood cancers will impact how we screen and follow clonal hematopoiesis in the foreseeable future and integrate preventative efforts long term for breast cancer and other solid tumors.