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LETTERS TO THE EDITOR

Could Clonal Hematopoiesis Explain the Link Between Increased Cancer Mortality Incidence in Heart Failure?

We read with interest the paper from Bertero et al[1] that compared the incidence of cancer in a cohort of 104,020 heart failure (HF) patients aged ≥50 years from Southern Italy with a similarly sized, matched cohort as controls. The study demonstrated a 76% higher incidence of cancer diagnosis in those with HF, and a 4-fold higher risk of cancer death, most pronounced in those aged <70 years.[1] This finding is not surprising because HF and cancer share many risk factors.[2] It is a challenge to ascribe anything more than an association between HF and cancer with retrospective, observational data, given the potential risk of confounding and absence of details regarding cancer treatment. However, clonal hematopoiesis (CH) could be a unifying underlying pathology that could partially explain these results.

CH is selective clonal expansion of acquired mutations in hematological stem cells.[3] Mutations in driver genes, such as *DNMT3A* and *TET2*, were found to be associated with an increased risk of hematological malignancies and an excess mortality not explained by malignancy alone, but rather CH conferred a higher risk of developing cardiovascular disease (heart failure, atherosclerosis) and adverse events (myocardial infarction, stroke, HF decompensation).[3] CH is more prevalent in those with HF and is associated with a 2-fold risk of HF hospitalization and death.[3,4] Moreover, there is a greater understanding of the role of CH in nonhematologic malignancy, whereby CH is associated with worse outcomes, greater relapse of malignancy, and mortality.[5] Notably, in the Bertero et al[1] study, multiple myeloma and lymphoma were the second and third higher risk cancers in HF respectively, potentially suggesting that CH could explain this relationship in hematologic malignancies.[1] Cancer therapy-related myeloid disorders could explain some of these findings, but other concerns include augmented immune function that may reduce the ability to clear cancer cells by T cells.[5]

We hypothesize that CH changes leads to an altered inflammatory state increasing the susceptibility of individuals to malignancy, HF, and other chronic diseases associated with aging. Determination of the frequency of CH mutations in HF patients may better elucidate the increased risk of cancer mortality, and provide a biomarker to risk-stratify HF patients, allowing closer surveillance in those at risk of HF and cancer adverse outcomes.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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