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EDITORIAL COMMENT

Heart Failure Post-Hematopoietic Cell Transplantation in Patients With Lymphoma

Another Piece of the CHIP Puzzle

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Over the last decade, somatically mutated hematopoietic stem and progenitor cells causing clonal hematopoiesis (CH) have been identified as a shared risk factor for cancer and cardiovascular disease (CVD).[1] Clonal hematopoiesis of indeterminate potential (CHIP), a form of CH detected via next-generation sequencing of DNA from peripheral blood with a variant allele frequency >2%, involves mutations in genes frequently associated with myeloid malignancies.[2] Although the risk of progression to myeloid cancer is low (0.5%-1% annually),[1] CHIP is associated with increased morbidity and mortality, likely due to accelerated inflammation-sensitive diseases,[2] including an up to 2-fold higher risk for atherosclerotic cardiovascular disease (ASCVD) and non-ASCVD like heart failure (HF).[1,3]

Despite a prevalence of over 10% in healthy individuals over 70 years,[1,2] clinical CHIP detection lacks test and variant standardization and does not influence treatment. However, among cancer patients, intentional and incidental CHIP detection has spurred interest in risk stratification.[2,4] Incidental CHIP detection occurs during cell-free, tumor, or "germline" blood DNA sequencing.[4] CHIP-related mutations provide prognostic insights for both the malignancy and cardiovascular risks in next-generation sequencing-profiled patients with myeloid cancer.[5] CHIP-related risk assessment has the potential to become important in cardio-oncology due to common features across cancers: higher prevalence than in the general population,[4] enrichment in DNA damage-response (DDR) genes following cytotoxic therapy,[6] association with anthracycline cardiotoxicity,[7] and worse overall survival.[5,8,9] However, there continues to be variability in CHIP's impact on primary malignancy outcomes and CVD. Furthermore, cause-specific mortality is driven by malignancy type, cancer therapy, and specific gene mutations. Therefore, focused studies on CHIP and cardiovascular risk by cancer type are essential to leverage these insights for improved clinical outcomes.[10]

In this issue of *JACC: CardioOncology*, Rhee et al[11] elegantly examine CHIP's association with incident HF among lymphoma patients undergoing autologous hematopoietic cell transplantation (HCT). They studied a retrospective cohort of 861 patients with Hodgkin and non-Hodgkin lymphoma and a median age 55.7 years. Using a standardized approach, CHIP was detected in mobilized peripheral blood stem cells before HCT in 21.6% of the cohort. This is a higher prevalence than expected in the general population (approximately 5%) and similar to prior reports in individuals undergoing autologous HCT.[6] The most commonly mutated genes included *DNMT3A*, and *TET2*, with frequent variants detected in DDR genes *PPM1D*, *TP53*, and *ATM*. This likely reflects enrichment of DDR clones or therapy-related CH following selective pressure on hematopoietic stem and progenitor cells from prior chemotherapy.[6] The study's

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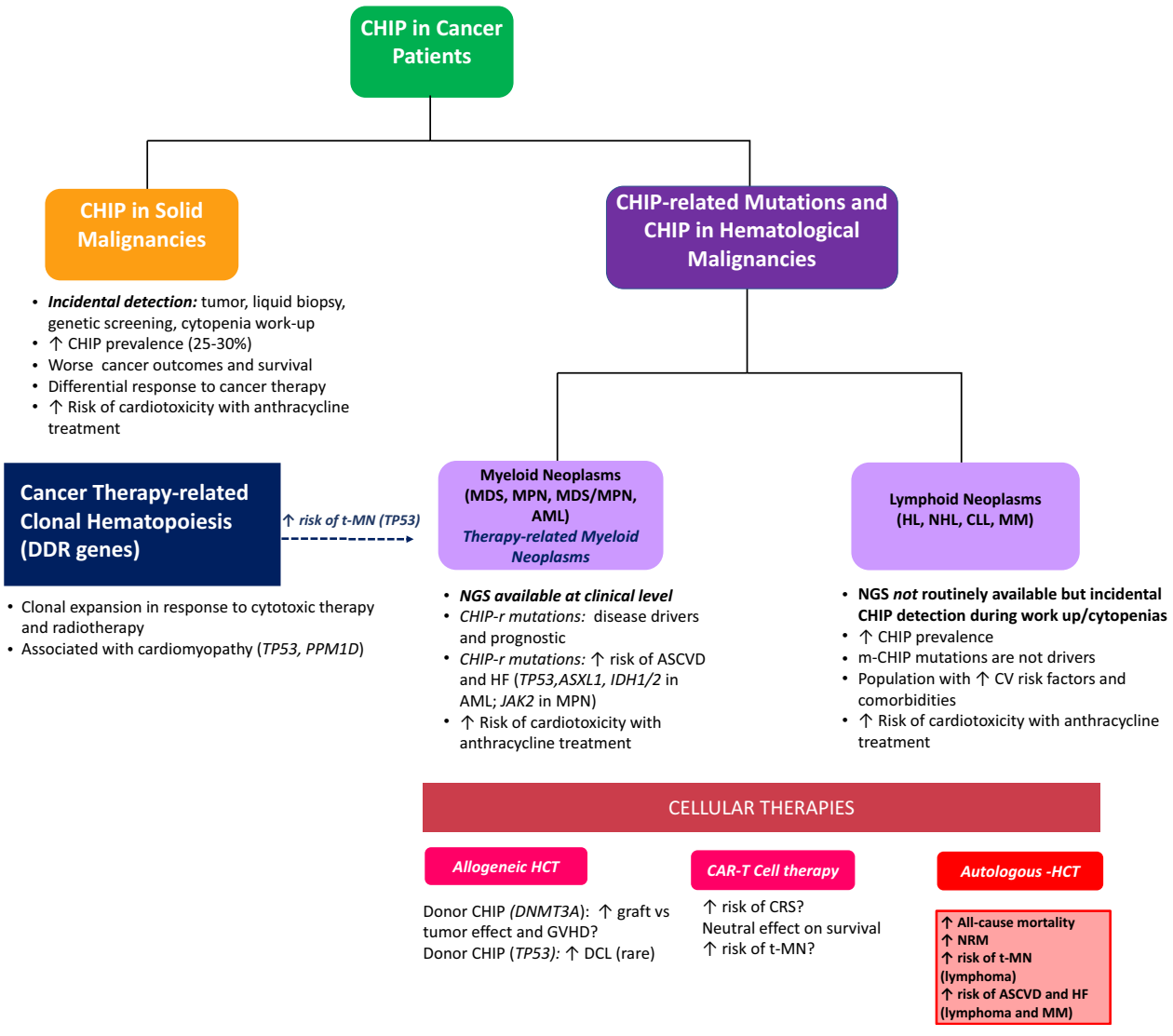
FIGURE 1 **An Overview of the Relevance of CHIP Based on Malignancy Type**



This figure provides an overview of clonal hematopoiesis of indeterminate potential (CHIP)-related cardiovascular and hemato-oncological risk in cancer patients. AML = acute myeloid leukemia; ASCVD = atherosclerotic cardiovascular disease; CAR-T = chimeric antigen receptor T-cell; CHIP-r = clonal hematopoiesis of indeterminate potential–related; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; CV = cardiovascular; DCL = donor cell leukemia; DDR = DNA damage-response; GVHD = graft vs host disease; HCT = hematopoietic cell transplantation; HF = heart failure; HL = Hodgkin lymphoma; MDS = myelodysplastic syndrome; m-CHIP = myeloid clonal hematopoiesis of indeterminate potential; MDS/MPN = myelodysplastic/myeloproliferative neoplasm; MM = multiple myeloma; MPN = myeloproliferative neoplasm; NGS = next-generation sequencing; NHL = non-Hodgkin lymphoma; NRM = non-relapse mortality; t-MN = therapy-related myeloid neoplasm(s).

key finding is the positive association of pre-HCT CHIP with 5-year incident HF, independent of clinically relevant covariates with a subdistribution HR of 2.48 (95% CI: 1.32-4.68). The investigators also confirm the previously reported association of CHIP in lymphoma patients with post-HCT nonrelapse-mortality.[9] This further emphasizes the clinical relevance of the association of CHIP with HF, since cardiovascular deaths were among the most common causes of nonrelapse-mortality. An important finding

of this study is the nearly doubling of incident HF with both hypertension and CHIP, potentially providing opportunities for risk modification. Lastly, the investigators performed exploratory analyses to further characterize CHIP-related HF risk. They noted an increased risk of incident HF among individuals who harbored ≥2 CHIP variants and in those with large clones (variant allele frequency >10%), as previously described.[2] Interestingly, patients with large clones had an ≈8% cumulative incidence of HF shortly after HCT, suggesting possible subclinical HF at time of HCT or residual confounding. It is also possible that early post-HCT atrial fibrillation, which is commonly associated with HF decompensation,[12] may play a role, particularly among those harboring large *TET2*-mutant clones.[13] In alignment with prior studies, *TET2* and *DNMT3A* variants were associated with incident HF,[3,6,14] whereas *PPM1D* mutations were not. Larger, adequately powered studies are required to examine individual gene-related HF risk.

The study is not without limitations. As in all retrospective studies, residual confounding cannot be excluded. Associations between conditioning regimens used in only 6% of the cohort and HF, suggest that CHIP$^+$ individuals may share other unmeasured outcome-associated factors. Incident coronary artery disease (CAD) such as myocardial infarction or coronary revascularization were not available as an outcome or as a time-varying covariate. Given the known causal association between CHIP and CAD[2,6] and CHIP/CAD with heart failure outcomes,[14] it would have been informative to account for incident CAD as a time-varying covariate or determine whether prevalent CAD is an effect modifier in stratified analysis, particularly since CHIP has been associated with ischemic cardiovascular death in patients with lymphoma undergoing autologous HCT.[9] Pre-HCT malignancy was also associated with CHIP in the present study (OR: 1.79; 95% CI: 1.12-2.84), but was not included in the multivariable models for the outcome of HF. Nevertheless, prior malignancy was accounted for at least partially via inclusion of comorbidities in the models.

Despite limitations, this study's findings are robust and suggest CHIP should be considered a risk factor for HF in lymphoma patients undergoing HCT. However, CHIP testing outside of trials or studies is not yet shown to improve outcomes. The 2022 ESC cardio-oncology guidelines recommend echocardiography at 3 and 12 months after HCT in high-risk patients,[15] aligning with the study's median HF onset of 6 months, indicating patients with incidentally detected CHIP may benefit from similar surveillance. However, the effects of CHIP should not necessarily be extended to other forms of cellular therapies. For instance, donor-engrafted CHIP in allogeneic-HCT and pretherapy CHIP in CAR-T therapy may enhance antitumor effects, potentially affecting cardiovascular outcomes indirectly via graft vs host disease or cytokine release syndrome, respectively.[16,17] This again highlights the complexity of CHIP in cancer patients (**Figure 1**), and at the same time reinforces the clinical value of the work by Rhee et al[11] by phenotyping CHIP-related HF risk and interacting variables in patients with lymphoma undergoing HCT. Further research on malignancy- and therapy-specific CHIP risks will be essential for advancing CHIP as a precision medicine biomarker in cardio-oncology, with the goal of developing tailored surveillance and treatment strategies to improve outcomes.

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